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Resiliency to Stress Disorders: A matter of good-enough, prior exposure to stressors.

by

Angela S. Neil

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of

the requirements for the degree of Master of Education

in

Counselling Psychology

Department of Educational Psychology

Edmonton, Alberta

Spring 1996

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Angela S. Neil

52342 Range Road 211
Sherwood Park, Alberta T8G 1A7

January 2, 1996

University of Alberta

Faculty of Graduate Studies and Research

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Resiliency to Stress Disorders: A matter of good-enough, prior exposure to stressors submitted by Angela S. Neil in partial fulfillment of the requirements for the degree of Master of Education in Counselling Psychology.

J Mitchell

Dr. J. J. Mitchell

Ken Smart per D. Shannon-Brady

Dr. D. T. Shannon-Brady

Katherine L. Peters

Dr. K. Peters

Angela S. Neil

Voyage of the Personaut

In man as in animals, the physical and mental structure can be deeply affected only while the processes of anatomical and physiological organization are *actively* going on; the biological system becomes increasingly *resistant* to change after it has completed its organization. These statements are valid not only for anatomical and physiological differentiation, but also for the emergence of tastes, social attitudes, and even the perception of space in interpersonal encounters . . .

Prenatal, neonatal, and other early influences thus constitute a continuous spectrum through which the environment conditions the whole future of the developing organism.

Rene Dubos
In *So Human an Animal*

* *Italics the addition of thesis author.*

Dedicated to those who influenced my thinking on the nature of stress

David Neil
Patrick Neil
John Mason
Michael Meaney
Sigmund Freud

And to those who nurtured and guided my thoughts on stress

Liz Neil
Kathy Peters
George Buck

Abstract

This thesis includes a compilation of research evidence that supports the existence of an identifiable process in the development of vulnerability or resiliency to psychobiological stress related disorders. Exemplars of the research include studies of critical developmental periods in animals which have suggested that handling, rearing, and social-psychological stressors impact later stress responses and coping with disease (Post & Weiss, 1995; Meaney, 1993). As well, studies of human (adult) stress response disorders seem to suggest that prior experience with stress may effect the outcome of posttraumatic stress disorder in adults (Yehuda, Resnick, Kahana, & Giller, 1993). An integration and an extension of the findings of such studies have provided the basis for two postulations: (1) the vulnerability of the psycho-biological, neuro-endocrine, stress response systems may be established by either excessive or deficient early stress experience; and (2) resiliency may be established by developmentally appropriate ("prostress") experiences. These postulations are discussed in the context of improving our understanding of the human stress response systems and of potential applications within the areas of child and adult psychological development.

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Introduction

This thesis reviews evidence in support of the existence of a specific psychobiological process in the development of vulnerability* or resiliency* to stress disorders*. Some researchers attribute recovery from stress disorders to cognitive coping (e.g., hope, spiritual meaning, social connection, etc.). This is a form of resiliency that one can learn. In this thesis another form of resiliency is explored; the psychobiological changes that may occur to the stress response repertoire as a result of appropriate levels of stimulation ("prostress"*) during early development. A model for such a "prostress" process already exists and is being developed to prevent early-onset diabetes, a disorder which is considered to result from a genetic predisposition. The neuro-immune process of either resiliency or vulnerability to diabetes may provide a useful model for the general neuro-endocrine process of stress response resiliency or vulnerability.

The focus of this investigation is the development of stress coping mechanisms during the early developmental stages. Animal and human stress research is used in order to search for a more complete understanding of stress coping responses with emphasis on the correlation between stress responses and vulnerability to illness. Stress related illnesses like posttraumatic stress disorder (a mental illness) and autoimmune disorders (somatic illnesses) will be included. There are important new fields and interdisciplinary research projects discussed throughout this paper. These new fields and research projects are integrated with older established understandings of mind-body connections and stress response strategies.

Research into developmental periods of both animals and humans indicate that handling, rearing, and psychological stressors impact on coping with disease

* *A Glossary of Terms & Concepts can be found after the Bibliography.*

or mental illness (Gold, Goodwin, & Chrousos, 1988; Lewis, Worobey, & Thomas, 1989; Meaney, 1993; Post & Weiss, 1995; Yehuda, Resnick, Kahana, & Giller, 1993). These findings allow speculation that we can improve our early care techniques to promote physical and mental health. In this thesis an attempt is made to show that by increasing our understanding of how the psychobiological system works and by using healthcare technology with greater discrimination, we can promote better health. In fact, technological interventions and traditions may contribute to health problems when combined with a lack of understanding of how these stress response systems develop and function. It is the belief of this author that as caregivers we are missing important developmental stages wherein care of neonates (birth - 28 days) could be improved. We are missing opportunities for improving our caregiving by not being aware of and implementing the relevant research from a variety of disciplines. The early stages of neonate development appear to be the time when maximum opportunity exists for promoting healthy responses to stress. The data reviewed in this thesis indicate that certain conventional child rearing practices especially during perinatal development may impede the development of optimal stress response repertoires.

The general postulations proposed herein are that too much stimulation (i.e., trauma*), too little stimulation (i.e., deprivation*), or good-enough stimulation (i.e., "prostress"*) during early development stimulates the pleasure-pain, neuro-endocrine centers and sets up a range of stress responses for future preparedness in the general environment. Stress responses may promote either vulnerability or resiliency to stress related illness. Psychological-neurological-immunological-endocrinological (PNIE) responses to stress are thought to be structural pathways and processes shaped by exposure to specific stressors

(Plotsky & Meaney, 1993). These PNIE responses may promote either resiliency or vulnerability of the organism during future stressful situations (Yehuda, Resnick, Kahana, & Giller, 1993; Post, 1992; Hunt, 1980; Kandel & Hawkins,1992). Stressors may include either 1) over-stimulation (e.g., chronic or acute trauma) or 2) under-stimulation (e.g., deprivations or neglect), both of which may initiate a process of increasing one's withdrawal from the stressors (e.g., avoidance responses, depression, anxiety) or increasing one's exposure to the stressors (stimulus / arousal seeking, certain addictive responses).

Stress responses are most likely part of a custom designed and self-balancing system, influenced by both heredity and environment. The actual stress responses used to bring the individualized system into balance may depend on individual constitution, personality and prior knowledge. When a stress response process is suppressed it may rechannel to the next available outlet in order to maintain equilibrium. For example, the smoker who gives up smoking begins overeating. Typically, our attention is brought to those individuals who exhibit "odd" ways of achieving this equilibrium. For example, adolescents or adults who have developed a compulsion or addiction (i.e., eating disorders, self abuse, or substance abuse) may seek a sense of pleasure or relief through either stimulation or relaxation. Thus, smoking could be stimulating or it could be relaxing. Interviews of those subjects who have successfully stopped smoking or drinking could help to determine if another pleasure / relief pathway has replaced the previous excessive behavior (addiction or compulsion).

Theoretically, if a pre-set PNIE stress response repertoire exists, a replacement pathway similar in type (relaxing or stimulating), in intensity (moderate or severe) and in orientation (physiologically, behaviorally, affectively and/or cognitively) would be sought first. Psychological and physiological profiles

could help to predict a satisfying replacement process for unwanted stress relaxation or stimulation behaviors like overeating or substance abuse. Replacement processes can be made internally with biochemical therapy (e.g., nicotine gum for the addicted smoker) or externally with behavioral or cognitive therapy. Ideally, a more biologically and socially adaptive replacement process could be found to fit each individual's type, degree, and orientation of addiction or compulsion. Rationale and support for the potential of psychobiological process changes is developed within this thesis. Psychobiological, in this case, refers to behavioral responses and neuroendocrine systems associated with stress.

This thesis includes a review of relevant research focusing on correlates among neonates' stress responses and among adults' stress responses to similar environmental stressors, especially responses that can persist over time and that can relate to stress disorders. Neonate and adult stress responses can be compared according to similar neuro-endocrine measures of emotional and physical stress in test subjects. The before and after neuro-endocrine changes are typically compared in the various studies between stressed and non-stressed, neonate and adult subject groups. The neuro-endocrine stress responses have already provided more direct measures of stress from the brain and the associated hormonal stress pathways (Jemerin & Boyce, 1990). This research has offered a more objective study of stress responses than measuring either behavioral or cognitive-affective experiences alone. The more each of these measures are used together (i.e., psycho-neuro-immune-endocrine measures), the greater is our understanding of stress as a process. A more complete profile is essential before treatment is prescribed. By observing the brain and body's mechanisms used for coping with specific stressors, we will be better informed as to when to enhance adaptive responses.

The first two chapters of this thesis discuss stress responses; Chapter 1 includes a brief description of stress responses and their developmental origins in humans and animals while Chapter 2 discusses the significance of possible types of stress responses in neonates and adults. Chapters 3 and 4 review current research on the variety of general and specific stress responses found within the different brain-body systems. The different systems are mentioned, with the focus on the neuro-endocrine system and related stress responses. The neuro-endocrine system is also found as a major focus within much of the contemporary stress research, in part, because it provides a new and interesting model, and because it can be monitored. For example, neuro-endocrine levels (i.e., stress related hormones and associated physiological responses) can be measured before and after specific environmental stressors have occurred, thus enhancing the reliability and validity of establishing them as standard measures of stress responses among specific groups or types of research subjects. In Chapter 5 an evaluation of the relevant research literature is presented; in Chapter 6 the general postulations are further refined and defined; and in Chapter 7 conclusions are drawn as to the importance and likely direction of further research questions. The research questions will be specifically outlined in the Conclusion. A Summary is presented to focus attention to the major points made by the author and a Glossary of Terms & Concepts is offered for clarification.

Chapter 1: Descriptions and Etiology of Stress Responses

Many researchers have explored the various steps involved in the stress reaction process. These steps can be described as follows; a stressor first affects the organism either externally (e. g., environmental, physical) and/or internally (e.g., somatic, emotional, cognitive), thus neuronally stimulating the body or the mind. This stimulation leads to further internal stimulation within the organism. With further nerve stimulation, the organism receives and/or perceives the stressor as brain stimulation that can now be termed stress. If the stress is adequately intense, this neuronal stimulation may generate a primary physiological stress response* in the organism. For example, stress stimulation affects part of the brain by activating neurons, such as the neurons of the reticular activating system which can activate the limbic system's hypothalamus and pituitary (Malven, 1993). Subsequently, specific parts of the body become stimulated from sympathetic neuron and/or pituitary-adrenocortical endocrine activation. The hypothalamus provides the structure where nerve transmissions are either transported through the body or translated into hormone releases which activate specific target organs *via* the blood (Malven, 1993). The primary physiological stress response may be brief. However, if this primary physiological stress response continues, or if brain stimulation due to perceived stress is intense, an organism may internally attempt to adjust back to a stable state through various physiological response systems. The sympathetic nervous system linked to the adrenomedullary (e.g., catecholamine) system forms a stress response pathway which is considered most responsive to acute emotional responses such as anger (Contrada, Leventhal, & O' Leary, 1990; Gray, 1971). Another stress response pathway, linked instead to the adrenocortical system, is the pituitary system (discussed more completely in

* *A Glossary of Terms & Concepts is provided after the Bibliography.*

Chapter 3) which is considered most responsive to chronic stress, anxiety, and depression or "situations that call for effort but for which control is not possible" (Smith, 1993, p. 45). If the primary physiological stress responses of general brain / body alert and readiness are successful, no further adjusting needs to be called upon by the organism to alter itself internally or externally. Secondary stress responses* (behavioral flight, fight, or freeze) are typically available to the organism and allow for further internal physiological adjusting (e.g., continued alert / readiness or relaxation). These responses may include externally expressed responses of behavioral, emotional, cognitive escape, or a self-directed change of the environment (e.g., a behavioral-emotional display of rage). In other words, the primary stress response is the brain and body under physiological readiness. The physiological and psychological demands made on the organism may require further secondary behavioral stress responses such as a fight, flight, or freeze.

Incidentally, the term 'freeze' does not appear to have been used in the literature to describe either an adaptive or maladaptive human stress response. However, the literature does accurately describe this response as an adaptive technique used by many wild animals (e.g., the prey 'freezes' to avoid notice by a predator). The term 'freeze' may be accurate for the behavioral and psychological descriptions of humans experiencing "hopelessness" (personal communication with "hope" researcher at the University of Alberta , Jevne, 1995)

Some researchers believe that many of the secondary options just listed are less obvious, or not at all available developmentally to the neonate until greater developmental integration has occurred (e.g., Als, 1983). Lacking this integration which increases stress response options, neonates would have mostly physiological responses to stress until they were developmentally mature enough for more

complex motoric, emotional, and behavioral responses. Healthy, full-term neonates may take several hours (or more) before they are capable of some coordinated and interactive behavioral responses to stressors, while premature neonates are usually capable of only physiological responses to stressors (Peters, 1995, personal communication). Thus, the internal physiological responses to stress may be all that is available for many newborns and this lack of options to reduce stress may make it difficult to stabilize their internal levels of stress at the best of times.

In terms of the etiology of stress, researchers and caregivers need to seriously consider the potential impact of high stress levels during critical developmental stages and any persistent or long-term effects that may result from high levels of internal stress. Due to the internal levels of stress being less observable in neonates (unless closely monitored) and our recent awareness of the impact of environment on neonate development particularly impact on stress response systems, this may be a new field requiring focused attention and more immediate investigation.

The early stress research literature (1950 - 1970) was initiated with studies concerned with general human and animal stress reactions (e.g., Cannon's General Adaptation Syndrome). The more recent studies combine stress research with theories on individual differences and new research on response system differences. This transition from a general stress response to a specific, individually unique response may typify the transition from theories of an observed, simplistic, general stress response to measurable, specific stress responses. This transition is due, in part, to advances in the technologies for stress response measurements.

The debate between general versus specific stress response is similar to the nature - nurture debate, in that both sides of the debate hold some truth and can both be applied in appropriate combinations under specific circumstances. A

holistic perspective of both the nature - nurture and the general - specific debates was concisely expressed by Kagan (1989). Along with colleagues, Kagan has investigated specific traits of shyness which they reported as childrens' initial behavioral reaction to unfamiliar events, such as extreme inhibition, behavioral restraint, quiet, and social avoidance with correlated extreme physiological reactions, such as increased heart period variability, pupillary dilation, norepinephrine activity, cortisol levels, frequency and pitch or vocal utterances. Kagan and colleagues reported that such a holistic approach and profile has influenced their explanation of inhibited behavior in early childhood.

> We believe that the actualization of shy, quiet, timid behavior at two years of age requires some form of [general] chronic environmental [nurture] stress acting upon the original temperamental disposition present at birth [nature]. Some possible stressors include prolonged hospitalization, death of a parent, marital quarreling, or mental illness in a family member (p. 162) . . . The recent research on temperamental types awards considerable [specific] influence to brain chemistry. (pp. 140-141)

It seems that Kagan resolves the general - specific stress response debate by suggesting that the stress experience is at first a general response and then, due to temperamental disposition and brain chemistry the chronic stress response becomes specific and individualized into shy or "uninhibited" behaviors. Shyness seems to be a predisposed trait that requires chronic or traumatic environmental precipitation. The biological precursors for shyness can be identified early in the first year of life which may be due to a genetic predisposition (or as proposed by this author, may also be due to prenatal or postnatal environmental experiences)

but the actual expression of shy behavior requires environmental stimulation. Not all one-year olds identified by Kagan with psychobiological precursors for shyness express shyness as a stable trait.

Researchers have described critical periods in animals as a time when environmental input enhances or inhibits the various active neuroendocrine pathways developing during that particular time period.

> Therefore, the question then becomes not *whether* environmental circumstances can alter dendritic growth, but *how early* in life it occurs. What is not known is the developmental stage at which the arrangement of synapses becomes more of a function of input stimulation (epigenetic [phenotypic] stimulus) than the result of a predetermined coded growth pattern (genetic stimulus). (Peters, 1995, p.18)

Many developmental texts state that the human central nervous system has developed primary structural connections and initial functional activities by the 24th post-conceptual week (the 37th week is considered a full-term birth). The more persistent structural pathways are determined in part by functional competition and sensory feedback mechanisms. The impact of environmental stimuli or stressors are, indeed, critical (if not essential then important) during the highly sensitive periods of development. Peters further describes the critical developmental process and the neuronal etiology of variations in stress responses.

> In animal models, the mechanisms which lead to developmental distortions are active inhibition or suppression of normal pathways through over activation of currently functional pathways. These pathways, in turn, lead

> to less differentiated and less modulated later overall functioning (physical, behavioral, and cognitive) . . . Contrary to what has been postulated in the past, premature infants' brains are overly sensitive and at the mercy of sensory information. The brain appears unable to buffer its intake due to a lack of inhibitory controls thought to be connected with the differentiation of higher associate cortical areas. (Peters, 1995, p. 3)

This quote helps to clarify the etiology of stress disorders by describing the possible neuronal mechanisms that are leading to developmental distortions of pathways which can include the stress response pathways. Developmental distortions can lead to persistent functional problems compounded or reduced by further environmental impact. This author is concerned that the appropriate levels of stress, otherwise called "prostress" experiences, are being offered during foundational developmental periods when the stress response pathways are being constructed and may be more vulnerable to environmental input.

The above discussion alludes to some of the negative and positive features of plasticity* (discussed further in Chapter 5) believed to be more obvious and lasting for longer periods in humans than in animals (Lerner, 1986). The disadvantages of plasticity are the vulnerabilities of developmental pathways to disruptive environments for longer periods during development. However, plasticity also affords some advantages for humans entering into specifically demanding or undemanding environments. One might wonder what happens to neonates overprotected or underprotected by technological advances from the important environmental stimuli which affect the associated developing pathways (e.g., immune, endocrine, neural, etc.)? Further food for thought might be why do

Neonatal Intensive Care Unit (NICU) babies (Peters, 1992; Herzog, 1983; VandenBerg, 1982) and forgotten orphanage babies (Hunt, 1980) rank so highly among the groups predisposed to learning and behavioral disorders (Yoshikawa, 1994; McGee, Silva, & Williams, 1984; Greenberg, 1983; Hunt, Tooley, & Harvin, 1982).

The prevention of some physical, psychological, and emotional disorders may be possible by providing appropriate levels of stimuli and stressors during early development. This author believes that an improved understanding of the etiology of stress responses can provide methods that are effective in the prevention of many early-onset stress disorders. For example, recent animal research is providing evidence linking the mechanisms for pre- and post-natal environmental stressors to human adult disorders, which range from the physical and behavioral to the cognitive and emotional impairments (Post & Weiss, 1995; Reul et al., 1994; Meaney, 1993; Gold, Goodwin, & Chrousos, 1988; Sapolsky, Krey, & McEwen, 1986; Kandel, 1983; Zarrow, Campbell, & Denenberg, 1972). The first three, more recent references just cited will be described and discussed in the following chapters.

Several earlier views on the etiology of stress and mental disorders also support the impact of environmental stressors on psycho-biological mechanisms.

> Kandel shared Freud's view that all mental disturbances must fundamentally be biological in nature. Environmental factors, such as genetic / constitutional characteristics and infectious or toxic [noxious] agents, affect the mind at the level of brain function . . . experience appears to modify brain function through altering synaptic strength and regulating gene expression . . . (Gabbard, 1994, p. 16)

Van der Kolk (1987) suggests that, "there is also evidence that the number and nature of brain receptors for particular neurotransmitters can continue to change throughout a person's lifetime. . . Thus it is conceivable that receptor changes induced by early deprivation or trauma in the [central nervous system] can to some degree be modified by later life experiences" (p. 50).

While neurotransmitter receptors may have some plasticity to up- and down- regulate (Wonnacott, 1990) the actual numbers of receptors with which we leave childhood may be more rigid (Meaney, 1993). It may also be possible that the structural pathways and feedback loops of the stress responses may be pre-activated and set in early developmental stages (pre- and post-natal) and thus, are less plastic processes later in life. This may offer a current explanation for Freud's belief that much of the later adult disorders were pre-set by early life experiences, leaving one vulnerable or resilient by the ages of 3 to 5 years. Next, in Chapter 2 is an in-depth discussion of the potential significance and implication of stress responses.

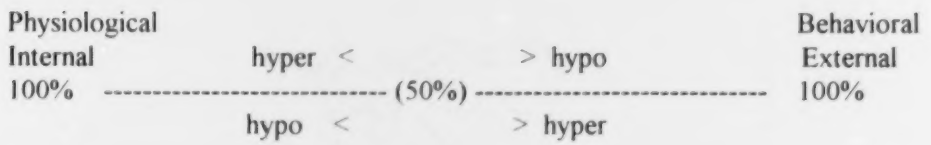
Chapter 2: Significance and Implications of Stress Responses

Stress is a common psychological and physiological experience, part of being alive and interacting with the environment. Sometimes the environment produces stressors that provide over, under, or good-enough stimulation appropriate for the individual and developmental period. An over-stimulating stressor for one individual may be either good-enough or far-too-little for another individual who is less responsive to stress. For example, researchers studying adult human individual differences in response to stressors have found two broad categories of responders: 1) "Sensitizers" are subjects who feel and express their stress experience consciously and verbally with fewer physiological repercussions; and 2) "repressors" are those who unconsciously have strong physiological responses to stress which they find difficult to identify and/or express (Cook, 1985; Shipley, Butt, & Horwitz, 1979). However, this research is influenced by a design weakness revolving around difficulties with the accuracy or reflection of self-reports of thoughts and perceptions of stress when compared to physiological responses of stress. The study of neonate responses to stress can include physiological responses which are internally monitored (e.g., heart rate, blood pressure, cortisol levels, etc.) or behavioral responses which are externally monitored (e.g., motor activity, vocalization, state of alertness, etc.). Both methods of stress response monitoring tend to obviate the self-reporting difficulties of accuracy and the addition of complex response dimensions of thoughts and perceptions of stress. The study of neonate stress responses may facilitate the search for the developmental origins of individual differences in the stress response and any resulting resiliency or vulnerability to psycho-biological stress disorders.

Health care effectiveness may be improved if we monitor neonates for their

responses to external stressors. These responses may lie on a continuum with the extremes identified as either hyper (greater)-stress responsive neonates or hypo (lesser)-stress responsive neonates, depending on whether they manifest stress internally (physiologically) or externally (behaviorally) (see Fig. 1).

Figure 1. A theoretical range of possible stress responses on a continuum.



If, by observing behavioral and emotional responses and monitoring physiological responses, we were able to learn more about neonates who are hyper-stress responders then perhaps we could learn to more appropriately comfort and treat them. If extremely stress responsive, the young hyper-stress responders may be refractive to external assistance and difficult to raise and teach. On the other hand, hypo-stress responders may also be difficult to work with, especially if they have intense physiological (internal) responses which are less easily observed.

There may be those hypo-stress responders, who internally or externally, perceive and/or express less stress and they may be better suited constitutionally to our increasingly stressful, highly, technical environments or they may have deficits that early detection would help to improve. It may be these extreme stress responders, externalizing and/or internalizing their stress, who experience the most frequent or intense, persistent neuro-endocrine changes in response to excessive or deficient environmental stressors.

If we were more alert, and monitoring for the possible existence of these types of stress responders (i.e., externalizers or internalizers), could we prevent specific stress response maladaptions or vulnerabilities? One important example of stress response maladaption with internalizer traits (e.g., alexithymia described in detail by Krystal, 1988; described on p.38) is, Posttraumatic Stress Disorder (PTSD). It has recently been reported that PTSD sufferers typically have had a prior history of severe stress and present persistent physiological changes consistent with vulnerability to future severe stress (Yehuda, Resnick, Kahana, & Giller, 1993; discussed more fully on p. 42).

If we consider that approximately 25-30% of the people who experience a traumatic stressor (e.g., war, torture, rape, accident or violent event, etc.) are diagnosed with PTSD (Breslau, David, & Andreski, 1991; Munck, Guyre, & Holbrook, 1984), the question becomes: what about the 70-75% exposed to similar trauma who did not develop or report PTSD? Many researchers attribute recovery, hardiness, resistance, or resilience from trauma to cognitive coping (e.g., hope, spiritual meaning, social connection, etc.). These are forms of resiliency that humans can learn or experience. For example, Kobasa, Maddi, and Courington (1981) have described hardiness as consisting of three cognitive characteristics found in adults: (1) control, or a belief in a personal ability to influence events; (2) commitment, or an approach to life marked by curiosity and a sense of meaningfulness; and (3) challenge, or the expectation that change is normal and stimulates development. This author views cognitive factors as potentially positive or negative stressors that contribute to resiliency or vulnerability and become increasingly more important later in human development.

Another researcher brings the psychological aspects of resiliency or vulnerability closer to the perspective taken in this thesis. Antonovsky (1979) has

identified the importance of environmental factors called "resistance resources" which can offer stress protection to humans. Resistance resources can include political, economic, educational, geographical, family, or social factors in the environment. Such research widens a perspective of the environment from one that limits the view of the environment to a hostile, continuous source of negative stressors. Instead, the view is widened to one where environments can be assessed for protective stressors / resources, deficient stressors or deprivations, and traumatic stressors. This more inclusive picture of the variety of environmental stressors supports this author's use of "prostress". Prostress (as defined in this thesis) can occur when a stressor from the environment provides an appropriate stimulation (or experience of stress) which alters the psychobiological stress response repertoire and enhances resiliency to future stressors.

Recent research of human infant stress responses (which include physiological and behavioral assessments) have focused on family "resistance resources" like maternal separation and bonding and the effects on infant attachment and coping behavior patterns (Gunner, Porter, Wolf, Rigatuso, & Larson, 1995; Hertsgaard, Gunner, Erickson, & Nackmias, 1995; Lewis & Ramsay, 1995; Spangler & Grossmann, 1993). For example, cortisol levels were found to increase as attachment behaviors were increasingly inadequate or coping resources were increasingly unavailable. These findings were in support of the earlier findings (Main & Solomon, 1986, 1990) that infants with disorganized or disoriented attachment behaviors (Type D infants) lack coherent stress coping strategies as compared to securely attached or insecurely attached infants. The "Type D [infant] attachments are expected to be most prevalent among infants who are at risk for poor parenting, or whose lives are characterized by a high degree of familial stress (Carlson, Cicchetti, Barnett, & Braunwald, 1989)"

(Hertsgaard et al., 1995, p. 1101). Cortisol levels are thought to be particularly valuable in attachment research because this aspect of the neuroendocrine system is believed to be stimulated when coping behaviors are inadequate and/or coping resources are unavailable (Gunnar, Marvinney, Isensee, & Fisch, 1988). Most relevant to this author's postulations are the findings that postsession cortisol levels measured to determine stress recovery after exposure to maternal separation and strangers in a lab are lower for insecurely attached infants than those of Type D infants and yet higher than those of securely attached infants who possess the most effectively organized stress response behaviors and lowest cortisol levels and quickest stress recovery (Hertsgaard et al., 1995). After 6 months of age, the cortisol levels have been found to stabilize through the maturation of the neuroendocrine system, becoming similar to adult diurnal cycling patterns, and accurately reflecting stable individualized temperamental differences (Lewis & Ramsay, 1995). It is postulated here, that securely attached infants may be exhibiting "prostress" response patterns from prior mild stress experiences, and Type D attached infants may be exhibiting vulnerability from prior severe traumatic experiences, while insecurely attached infants may be exhibiting the stress response patterns of deprived or not good-enough prior stress experiences (discussed more fully on pp. 31-32).

This thesis includes a look at the impact of protective, deprivational, and traumatic stressors on the psychobiological development of neonates. In other words, the focus here, is on an aspect of resiliency and vulnerability which is, *the psychobiological changes that may occur to the stress response systems repertoire as a result of excessive or deficient stress stimulation during early development*. Psychobiological changes may maximally occur when the neuro-endocrine pathways are developing and are more susceptible to environmental stimulation or

deprivation. Disruptive or maladaptive changes to a stress response pathway may also occur at any developmental period, whether genetically or environmentally induced. Prevention and early detection of maladaptive stress responses can promote health for more individuals than treating stress disorders *after* damage has occurred. These ideas will be more fully developed and supported in the following chapters.

Chapter 3: General and Specific Stress Responses

An initial study of general stress responses is Cannon's 1929 theory of the *fight-or-flight* stress response, an organism's response to a threat that has disturbed the physiological balance (e.g., body temperature, blood pH, plasma levels of sugar, protein) (Smith, 1993).

Cannon (1929) and Selye (1956) were physiologists who identified what occurred internally when an organism was stressed by the demands of an external threat. Cannon identified activation in the sympathetic nervous system and a hormonal discharge in the adrenal glands as causing a multitude of autonomic nervous system changes that prepare the body for *fight-or-flight*. Cannon also proposed that everyday pressures and worries, could activate the *fight-or-flight* response and lead to physiological imbalance and physical illness (Cannon, 1929).

Selye (1975) coined the term "stressors" to clarify that the environmental stimulus is separate from the internal experience "stress". Stress was defined by Selye as a "nonspecific result of any demand upon the body" (Smith, 1993, p. 8). Further, Selye differentiated between "eustress", positive demands upon the body and "distress", negative demands (Selye, 1975). It should also be noted that Selye furthered Cannon's mammalian *fight-or-flight* response with his description of the General Adaptation Syndrome (GAS). The GAS identified three stress response stages: 1) alarm occurs when the body is prepared for quick activity by a large-scale, physiological, resource readiness; 2) resistance occurs when the resources needed for adaptation are mobilized; 3) exhaustion occurs when maintenance resources are depleted and the body prepares again for large-scale readiness. Under extreme stress, one can experience severe alarm (shock), due to a massive sympathetic nervous system response, which leads to resistance or exhaustion, and sometimes death. Selye also believed (depending on the frequency and the intensity

of the stressor and intensity of the equalizing response) the physiological result could lead either to adaption or maladaption (including illness or death) (Feist & Brannon, 1988).

Many variations to Selye's stress response theory have since been introduced. Mason (1971, 1974) criticized the non-specific nature of the stress response to any noxious stimuli and suggested that emotional stress is the most potent of all stress experiences, causing the most intense physiological stress responses in both animals and humans. Mason proposed that the stress response is specific to emotional stressors since, "emotional stimuli rank very high among the most potent and prevalent natural stimuli capable of increasing pituitary-adrenal cortical activity" (Mason, 1975a, p. 23). Interestingly, it is the pituitary-adrenal cortical (PAC) pathway, activated by emotional stimuli that Cannon and Selye first identified as part of the general, physiological response to stress. For example, Cannon's general theories seemed to have originated in the early study, "Emotional stimulation of adrenal secretion", (Cannon & De La Paz, 1911). It appears that Cannon and Selye took the specific data on emotions to support a generalized theory which emphasizes that stress is the response to stimulation that includes physiology and emotions (Feist & Brannon, 1988). Mason (1971) defined stress as the response to stressors that always includes emotions (without emotions the event is not a stressor). Now, we tend to accept that there are a variety of neuronal stress response pathways for the various types of stressors (e.g., physical-hemorrhage, psychological-fear, etc.), (Plotsky & Meaney, 1993). These specific pathways (discussed in Chapter 4) are also believed to "communicate" with each other and to be modifiable over time thus contributing to individual differences in stress reactions (Plotsky & Meaney, 1993; Kandel & Hawkins, 1992).

Mason (1971) presented an important concept in the theory of emotional specificity and the stress response. If Mason is correct in proposing that the general stress response always includes emotional system involvement, then the psycho-neuro-immune-endocrine (PNIE) pathways are likely to be included in any general stress response (i.e., general adaptation syndrome). According to Mason and Contrada, Leventhal, and O'Leary (1990) the emotional stress response system (i.e., limbic system) appears to activate the PNIE pathways.

It is interesting to follow Mason's (1971) examples of physical stressors (e.g., hemorrhage, cold, starvation) with underlying emotional components and then reconsider current research of physical stressors and include possible unassessed emotional contributors to the studied stress responses. For example, diabetic mice and rats given adjuvant therapy (a small immune stressor) to prevent diabetes, were possibly given other stressors, up to now not mentioned, in addition to the physical immune stressor. Other stressors may have included permanent maternal separation at weaning which is a sudden physical and/or social - emotional stressor. Another general stressor could be the complete body dip in a bleach solution which was used to increase the germ-free status of the research animals. This would add another physical and emotional shock if the water is cold and if the bleach is concentrated. Further, if the rats have never been exposed to open water the body dip becomes a novel and sudden stress. It is interesting that, though almost 100% of the original test subjects were permanently diabetic-free, this has not been replicated since the early research noted by Sadelain, Qin, Lauzon, and Singh (1990). This may be due to the body dips into any solution not being repeated. Immune stressors (e.g., antigens) alone, do not produce 100% permanently diabetic-free mice or rats according to Sadelain and colleagues (1990). Something appears to be missing. Could it be that a bleach dip bath at

weaning time is an important activation of not only the immune system, but includes a rewiring of the general stress response systems (i.e., psycho, neuro, immune, endocrine)? It may be that each of these systems can be singled out or that smaller groups of stress response systems may be activated under certain circumstances. Activation of the full stress response repertoire might not be required unless emotions are also stimulated. Both specific and general stress responses could thus exist separately; 1) a specific stress response can occur without the emotionally connected systems (e.g., a specific immune stress response, or a physiological response to hemorrhage, as noted by Plotsky, Thrivikraman, and Meaney, 1993); 2) other specific stress responses, require or include emotional arousal to stimulate the PNIE stress response systems.

There is speculation that the incidence of autoimmune diabetes (Type I) as a specific stress response disorder is higher in the more technologically advanced countries where complete Freund's adjuvant is not always mixed into the childhood immunizations. Thus, these neonates are not given a mild, good-enough stress stimulation of the PNIE systems. In other words, these neonates do not receive an important generalized, stress repertoire conditioning in the mild to moderate range ("prostress") when they do not receive the Freund's adjuvant. Freund's adjuvant is preferable to far-too-little (deprivation) or far-too-much (trauma) stimulation of the immune system at the critical developmental time period. "CFA [Complete Freund's Adjuvant] is a strong immune adjuvant and is likely to have widespread effects on immunoregulatory circuits" (Rabinovitch et al., 1995). "...Adjuvant administration may mimic or amplify protective effects of certain environmental factors" (Sadelain et al., 1990) which modulate the penetrance of diabetes in otherwise genetically diabetes-prone individuals. The implications are that Freund's adjuvant provides an appropriate "prostress" generalized stimulation of the

immune system which prevents the onset of Type I diabetes.

Chapter 4 : The Variety of Brain-Body Stress Response Pathways

Stressors have been separated into different categories according to which parts of the central nervous system are stimulated or which neuro-endocrine systems and feedback loops are involved (Smith, 1993). There appears to be a variety of possible stress response systems and feedback loops, and they may be specific to each (or types of) stressor(s) (Plotsky, Thrivikraman, & Meaney, 1993; Levine, 1988). According to Plotsky, et al., (1993),

> Because neural input-encoding qualities of individual stressors utilize, in part, stimulus-specific pathways, the effectiveness of glucocorticoid negative feedback in modulating ongoing and subsequent activity of the hypothalamic-pituitary-adrenal (HPA) axis is dependent on the type of stressor and the nature of the neural pathways mediating the initial activity. (p. 59)

The following quote from Smith (1993) provides further support for a variety of specific stress response pathways,

> There is considerable additional evidence for the specificity of the stress response. For example, the response of the heart to stress can vary depending on whether coping is active or passive (Obrist, 1976), or avoidant or vigilant (Lacey & Lacey, 1978). In addition, different patterns of stress hormone secretion are linked with worry versus denial (Mason, 1975 a) and anger versus fear (Ax, 1953). (p. 45)

Rutter (1988) describes this in another way,

> . . . more recent experimental studies with animals have extended the range of stressors to include events that cause arousal as a result of novelty, uncertainty, or unpleasantness, but not necessarily as a result of physiological threat or challenge (Hennessy & Levine, 1979). Similarly, human studies with adults have dealt with a variety of life events such as examinations, parachute jumping, admission to the hospital, wartime combat, and various fear-evoking stimuli (Cox, 1978; Rose, 1980). (p. 6)

Thus, it appears that a variety of specific stress response pathways are being considered in the research literature. Different stressors evoke different stress responses.

What follows is a brief description of internal stress response pathways meant to inform the reader of the current understandings of the stress response repertoire. Each pathway is important for a holistic view of stress response malfunction or function. The following five physiological stress response pathways are believed to intercommunicate and result in adaption and health or maladaption and illness.

1. The sympathetic-adrenomedullary (SAM) pathway includes the activation of the sympathetic portion of the autonomic nervous system *via* the 'stress trigger', the posterior medial hypothalamus. The posterior medial hypothalamus releases brain hormones called neurotransmitters which activate the inner medullary region of the adrenal glands through a series of neural impulses. The adrenal glands release catecholamines (i.e., epinephrine, norepinephrine) into the bloodstream, reinforcing the nervous system's overall alert of the body but with

slow, longer-lasting action. This longer lasting response constitutes the *fight-or-flight* response to acute stress and is considered to be Selye's first GAS stage, *alarm* (Guyton, 1991).

2. A pathway related to the SAM pathway is the parasympathetic rebound response which is the alert reduction of the brain and body via the autonomic nervous system. Selye included this response in his *exhaustion* stage. If the stress response recovery is activated too soon, too late, too intensely, or not at all, then the result could be unwanted behaviors, depression or death (Feist et al., 1988). For example, the parasympathetic (stress recovery) responses of: 1) involuntary urination or defecation during fear and excitement (Smith, 1993); 2) "voodoo death" (Cannon, 1942), the parasympathetic rebound from extreme sympathetic shock and/or the perception of no-escape or hopelessness (Kalat, 1984); and 3) the perception of no-escape and resulting depression (Smith, 1993).

3. The pituitary-adrenocortical (PAC) pathway, which is part of Selye's second GAS stage (called *resistance*), becomes involved when stress is chronic. According to Smith (1993), this PAC pathway (also called the hypothalamic pituitary adrenal, HPA pathway or axis) is activated by the hypothalamus when stress is experienced continually and the body can no longer remain in the "alarm readiness" stage. In such a case the hypothalamus releases corticotropin-releasing hormone (CRH), a neurotransmitter which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). Adrenocorticotropic hormone (ACTH) travels in the blood to the outer cortex of the adrenal glands where up to thirty stress hormones can be released (Smith, p. 39).

One important group of adrenocortical hormones, the corticoids, are often used to indicate the level of chronic stress within an organism. Glucocorticoids,

however, are only one type of corticoid (the mineralocorticoids are another type). Due to its direct connection to the immune system's resistance or vulnerability to disease, cortisol is one of the most frequently studied glucocorticoids (Malven, 1993). Cortisol is also linked to complications with diabetes, atherosclerosis, heart disease, and decreased disease resistance (Smith, 1993; Mason, 1971). Another glucocorticoid, "17-hydroxycorticoid, appears to be related to subjective feelings of anxiety associated with stress" (Smith, 1993, p. 41). Much of the research on stress and its relationship to illness or disease includes data on glucocorticoid measures (some of this research will be described in forthcoming chapters).

4. Another internal stress response pathway is the immune system's response to pathogens and its weakening under other stress system over-loads (e.g., chronic psychological or physiological stress) (Borysenko, 1987). This pathway will be explained in depth in the following chapter.

5. The last group of pathways have only recently been defined. The peptide communication pathways are believed to connect all the above in addition to other pathways throughout the brain and body (Contrada, Leventhal, O'Leary, 1990). One group of peptides are the opiods (endorphins), the morphine-like peptides associated with natural pain reduction. Peptide research has demonstrated that stress responses can be conditioned therapeutically before or after the stressors causing pain. Opiod research, for example, has been designed to classically condition and/or psychologically activate the endorphins in order to produce a natural, self-regulation of pain through therapeutic activities like biofeedback training, mental relaxation, hypnosis-reregulation, and acupuncture (Smith, 1993).

It is important to note that any one of the pathways (SAM, parasympathetic rebound, PAC, the immune system, or peptides) could malfunction for a variety of reasons, leading to a maladaptive stress response.

Examples of possible maladaptions of the various systems may include over-activity, under-activity, or a lack of activity. Over-activity, describes autoimmune disorders from the aspect of self-destruction by one's own immune system (Wilder, 1995). This includes early-onset diabetes (discussed in Chapter 5). An over-active PAC pathway is postulated to be involved in the etiology of the chronic stress experienced by PTSD victims (Yehuda, Resnick, Kahana, & Giller, 1993). Examples of over-active stress responses exist among war veterans or individuals who appear to experience quick and indiscriminate startle responses to sudden and loud auditory stimuli (Eysenck, 1990; Kolb, 1987; Kandel, 1983; Shalev & Rogel-Fuchs, 1993). The startle response is also a symptom of PTSD sufferers, whether they were victims of torture, rape, accident, or natural disaster (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV). Under-active stress responses have been used as a theoretical explanation for psychopathy (Restak, 1979); described as an under-active response in the brain to harsh or irritating auditory stimuli despite verbal complaints to the contrary.

Chapter 5: Plasticity and Persistent Changes of Resiliency or Vulnerability

Some animals freeze or flee upon sensing danger while others react with fighting rage. Humans have a broader range of adaptive responses (i.e., cognitive, behavioral, and/or physiological) upon which to draw. This adaptive flexibility is referred to as *plasticity*. Plasticity* is thought to be greater in humans and higher-order species that demonstrate individually different responses whether adaptive or maladaptive (variations promoting resiliency or vulnerability) within similar environmental constraints (Lerner, 1976). This flexibility is often seen as genetically hardwired or environmentally learned, but researchers are acknowledging a greater frequency and variety of interplay between genetically and environmentally induced biological changes and adaptations (Defries, Plomin, & Fulker, 1994; Kagan, 1989). Such changes may have a late onset as in vulnerability to adult autoimmune disorders (e.g., Wilder, 1995) or a vulnerability established early in the course of development of the neuroendocrine system (e.g., immune vulnerability, Plotsky & Meaney, 1993; juvenile diabetes, Rabinovitch et al., 1995).

Vulnerability can be defined as a predisposition or an environmentally induced change in the brain-body processes that can leave the individual susceptible to developing a stress disorder or illness (Jemerin & Boyce, 1990). Environmentally induced vulnerability is thought to be a process occurring early in brain-body development. A vulnerability to stress disorders can result from insufficient stimulation or an inappropriate stimulation that leads to temporary, persistent, or permanent abnormal development (Colombo, 1982).

Early neonate development is a time when plasticity may be most active due to the greater number of neural connections being made and the associated

physiological systems being developed and integrated. Further evidence in support of plasticity exists in neurological research which describes the loss of extra unconnected (unused) neurons and synapses in the brain as a normal process in postnatal mammalian development (Anders & Zeanah, 1983; Changeux, 1985; Edelman, 1987; Mahoney, 1991). This period of loss is considered by some scientists to be a missed opportunity for a maximized connection of neurons that are apparently discarded when not stimulated (Changeux & Danchin, 1976; Erzurumlu & Killackey, 1982). Plasticity can involve increased neuronal connections (including synapses or receptors) due to their maximized ("prostress") use or decreased neuronal connections (including synapses or receptors) due to their understimulation or traumatic stimulation (Changeux, 1985; Hubel, Wiesel, & LeVay, 1977, Kandel & Hawkins, 1992; Post, 1992). MacDonald (1985) concludes that "plasticity is a ubiquitous but declining phenomenon across the life span" (Lerner, 1986, p. 206).

There is evidence for lasting neurological and endocrinological brain changes (that are either adaptive or maladaptive) due to environmental stressors or a lack thereof during early mammalian development (Pettigrew,1974; Hubel, Wiesel, & LeVay, 1977). Several researchers have reported that high levels of cortisol early in rat development have lead to neuronal death in the hypothalamus and hippocampus (McEwen, Gould, & Sakai, 1992; Meaney, Aitken, Bhatnagar, Van Berkal, & Sapolsky, 1988; Sapolsky, 1992). This loss of neurons is believed to affect memory and learning and lead to a vulnerability for cognitive impairments during aging (Meaney et al., 1988). "Postnatal handling [as a mild "prostress" experience] attenuates certain neuroendocrine, anatomical, and cognitive dysfunctions associated with aging" thus promoting resiliency in rats (Meaney, Aitken, Bhatnagar, & Sapolsky, 1990).

The following is an example of plasticity affecting the development of resiliency or vulnerability to high blood pressure disorders as a result of stress. Under extreme stress some neonates respond with increased blood pressure levels. Should such a state persist the neonates' blood pressure set point (the range of a normal blood pressure for each individual) will rise to a higher level. This can be adaptive for the healthy neonate trying to stabilize in a stressful environment. However, this physiological change (demonstrating the human potential for plasticity) can become maladaptive later in life as a higher blood pressure set point may no longer be necessary in a less stressful environment and/or may predispose the person to blood-pressure related complications (vulnerabilities). The premature, or otherwise weakened, neonate may more quickly succumb to the internal stresses of trying to adjust to a higher blood pressure in response to external stressors and become further weakened and unstable (Peters, 1991, pp. 12-15).

Another example of human adaptability (plasticity) to environmental stressors which occur in early development, with persistent (not necessarily permanent) changes to an individual's stress response repertoire, are found in the immune system. By 12 weeks post-birth, a genetically sound human immune system can fully respond to an environmental insult (Peters, 1995, personal communication). The specific immune stressor (antigen) invading the body creates a specific immune system response (antibodies) which will remain as indicators that the body did once respond to an infection and is resilient and ready for another similar invasion with an even faster immune stress response. The immune system can be unprepared due to a lack of previous exposure to an antigen and thus be vulnerable or the immune system can be run-down by overuse or poorly functioning due to a variety of other stressors. This immune process model of

resiliency and vulnerability may provide similarities / analogies for a neuro-endocrine process model of the development of resiliency or vulnerability to stress (Post, 1992, 1995). Mason (1975b, 1975c) suggested that we view stressors as analogous to pathogens to which some individuals will succumb if they have not built up a resiliency. It was noted that the immune response is analogous to the stress response which varies according to the individual's susceptibility to stressors.

It also appears that the immune and neuro-endocrine systems are interconnected and may develop processes and pathways in similar ways. A recent development in animal model research on the immune and neuro-endocrine stress responses measured in rats, indicates that postnatal environmental stressors (e.g., too little handling stimulation, too much handling stimulation, too much maternal separation) are important factors in creating persistent changes to individual stress response systems. Plotsky, Thrivikraman, and Meaney (1993) demonstrated this type of plasticity in mammals. Three groups of neonatal rat pups were either handled daily, handled and separated, or left undisturbed. The results (discussed next) offer an explanation for various systems involvements and responses to stress (i.e., psychological, neurological, immune, endocrine) which include resiliency or vulnerability to future stressors. Plotsky et al. (1993) demonstrated how the various PNIE systems were interconnected and effected similarly by stress. They were most interested in how social and physical stimulation during critical periods of development could enhance or impair the immune response to viral stressors when the same rats became adults. Even more exciting are their data indicating that; (1) the developmental period is critical, implying windows of PNIE plasticity (2) the type and intensity of the stressor experienced early in neonatal development creates a specific and persistent stress response, and (3) this contributes to the future responses to stress with a development of resiliency or vulnerability to stress

disorders. A similarity or interconnection between the immune and neuro-endocrine systems was found, in that the responses to stressors are specific and persistent, and based on the intensity of prior exposures which we find with the immune system and its building of immunity through inoculations. For example, the immune system creates pathogen-specific antibodies, while the neuro-endocrine system may create stressor-specific feedback loops involving specific synapses and receptors (Plotsky et al., 1993, p. 73). How the stress specific neuroendocrine feedback system's plasticity effect the levels of cortisol (and other stress hormones and peptides) produced in the development of resiliency and vulnerability remains to be delineated, but is currently under investigation (Meaney, 1993; Sapolsky, 1992). How the stress specific immune feedback system's plasticity effect the levels of antibodies (and other immune stress proteins and peptides like immunoglobulins and T-cell cytokine interleukins and interferons) in the development of resiliency and vulnerability, has been clarified by extensive research in the last decade (e.g., Rabinovitch, 1994).

What researchers seem to be finding is that cortisol production levels differentiate the individuals who developed resiliency or vulnerability. Low mean cortisol levels, high cortisol receptor numbers, moderate stress production cortisol levels with quick stress recovery back to baseline levels of cortisol are found among individuals with prior ("prostress") or appropriate experience of stress (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; Meaney, 1993; Yehuda, Resnick, Kahana, & Giller, 1993). Individuals who developed vulnerability due to prior (traumatic) stress experience, tend to have high cortisol mean levels, high stress production levels of cortisol, high cortisol receptor numbers and slower baseline recovery (Hertsgaard, et al., 1995; Meaney, 1993; Yehuda, et al., 1993). The individuals who experienced a deprivation of stress developed

vulnerability to later stressors which presents as high cortisol mean levels, low cortisol receptor numbers, high stress production levels of cortisol, and very slow baseline recovery levels of cortisol (Hertsgaard, et al., 1995; Meaney, 1993; Yehuda, et al., 1993).

In previously described research, extensive measurements were applied to neonatal rats receiving varied amounts of handling stress (Plotsky & Meaney, 1993). Results suggested that the first two postnatal weeks are a critical period for immune (Rabinovitch, 1994; Plotsky & Meaney, 1993) and neuro-endocrine changes (Plotsky & Meaney, 1993) which set up specific stress responses in both systems. Research indicates that the time period for human plasticity may last longer than in other mammals (Lerner, 1976, p. 108). Human neonates would probably not be restricted to such a short and critical period as neonatal rats. However, Kalat (1984) suggests that the advanced stages of cortical organizational development which occurs in humans may be part of a prenatal third trimester critical period of development (p. 278). Columbo (1982) prefers to call key human developmental periods "sensitive periods" rather than critical periods. The choice of using the terms critical or sensitive periods would depend largely on the degree of reversibility later in the human life span according to Columbo's arguments. Each human stress responsive PNIE system including the peripheral perceptual and sensory systems may have different windows of maximum environmental input periods and varying degrees of reversibility (Lerner, 1986; Erzurumlu & Killackey, 1982). Thus it is important to consider that the human period for environmental input to be incorporated into pervasive structural development may begin prenatally and extend well into the first year after birth. While this may offer hope for a longer period of flexibility it may also warn us of a longer period of exposed foundational system development between environmental stressors and the

continued building of stress system structures in humans.

It is the belief of this author that we can use the early developmental period to promote resiliency to stress disorders (e.g., secure childhood social attachment, p. 17, prevention of juvenile diabetes, p. 22) or we can ignore this period and unwittingly facilitate increased vulnerability to stress disorders some of which appear later in adult life (e.g., PTSD, insecure or disorganized childhood attachment, hypercortisol damage to limbic structures, adult autoimmune disorders like adult diabetes, stress related high blood pressure, and cardiovascular disorders, Frankenhauser, 1983).

The following is a discussion on the problems encountered while conducting research on plasticity. Controlled research that alters plasticity (of psychobiological structures) is not ethically feasible in human neonates. Instead, stress researchers extrapolate research results from animals to humans or extract limited data of retrospective research on humans exposed to traumatic stressors. These extrapolated and comparative leaps and limitations can be supported somewhat by animal research that provides sound correlational data between age groups and by prospective studies of animal neonates followed through into adult stages when stress disorders may become more obvious. Preferably, such research could be carried out with humans. However, one advantage of using animals is to conclude the project with postmortems which can provide information about exact brain-body structure changes.

Stress researchers also make logical and comparative extrapolations between neonate research and adult research data. This leap can be bridged by looking for the associated physiological and behavioral stress response changes in human neonates that persist into adulthood. The ideal ethical research is conducted through studies in humans. However, such studies are considered by many to be

costly and time consuming. Instead, comparative studies between species and between age groups are used to examine the stress responses to specific stressors which mammals may share, and neonates and adults may share. The drawbacks of such comparative studies occur when the continuous and developmental changes of the same system, whether in one species or in one individual, have not been monitored from infancy to adulthood. But this points to the heart of the problem with research applications and generalizations. Thus, it is essential that those who use research data are aware of the extrapolations and problems with generalizations. Researchers must often make the best of less than ideal research circumstances. Another important example of less than ideal circumstances that applies to any prospective research between age groups (e.g., infancy to adulthood), are the myriad of variables which could effect changes that cannot be controlled for, especially in ethically conducted human research. Animal research gives somewhat more freedom to control variables which may alter the individuals health or life in a negative way (prospectively). In stress research, animals are frequently used to study vulnerability and the internal physical and physiological changes. Humans are often involved in controlled studies of resiliency factors, unless use is made of some unexpected traumatic or deprivational event when data is collected after the fact (retrospectively).

Yehuda, Resnick, Kahana, and Giller (1993) use animal research data as support for their studies of lasting, neuro-endocrine changes in adult human subjects with PTSD. Both groups of investigators (Plotsky et al.,1993 and Yehuda et al., 1993), show that prior exposure to stressful experiences (whether handling in rats; war or rape trauma in humans) alters the neuroendocrine and immune systems. Stressful experiences that alter the neuroendocrine system effect lasting changes in PNIE pathways and receptors which alter the stress responses

measured (i.e., glucocorticoid levels and numbers of their receptors). Yehuda et al. (1993), conclude that prior exposure to severe stressors, or a "previous stress history", sets up pathways similar to those found in subjects suffering from symptoms of PTSD. They theorize that a specific vulnerability to stress disorders (i.e., PTSD) is developed in the neuro-endocrine pathways if a sufficiently severe stressor has occurred earlier (p. 292).

Post (1992) uses retrospective research on humans and prospective research on animals to develop a theory on the etiology of emotional disorders from prior social stressors. Data is extrapolated and correlated between mammalian species (e.g., rats, monkeys, and humans) in order to describe the psychobiological mechanisms of vulnerability to emotional disorders based on prior exposure to emotional stressors. Post has demonstrated in rats that emotional stressors can set up specific PNIE pathways which can be triggered later in life by environmental cues. In rats, these pathways were delineated and found to become increasingly sensitive and interconnected with frequency of use. Eventually, these pathways no longer required external cues to trigger them but became internally triggered as if spontaneous. The pathways cycle faster and faster as the interconnections are actually seen to spread and grow in the brain tissues. Post has linked these fast cycling pathways to the bipolar cycling of depression in humans studied at the National Institute of Mental Health, NIMH. The findings of similar etiology, brain regions, pathways, and responses to drugs between rats and the bipolar depression in humans, studied by Post and colleagues, make the extrapolation of animal data helpful for delineating and treating severe manic depression in humans. Post's theory promotes the urgency of treating and stopping cycling depression before the brain pathways become so spontaneously sensitive and fast cycling that they are treatment resistant (both to psychotherapy and/or

drug therapy) (Post & Weiss, 1995).

Plotsky and Meaney (1993) demonstrate in rats the hypothesis of appropriate "prostress" (proposed in this thesis). They showed how appropriate (mild) stress experiences given early during psycho-neuro-immune-endocrine development can alter PNIE stress response systems for resilient responses to stress in adulthood. They found, that compared to non-handled, non-separated pups, the rat pups (2-3 weeks old) exposed to severe maternal separation or handling stress had maladaptive adult immune and neuro-endocrine responses to stress. However, the mildly stressed pups showed superior adaptive stress responses as adults (pp. 69-71). This provides evidence for the connection between the stress responses of the immune system and the neuro-endocrine system (from a presentation by Meaney during the September, 1993, University of Alberta, Heritage Fund Conference on Stress). Both systems can develop, through plasticity, maladaptive stress responses which can result in persistent vulnerabilities to stress disorders. If the immune and/or neuro-endocrine system are over-stressed or under-stressed early in development then maladaptive stress responses can result as well as vulnerabilities to stress disorders (mental and/or somatic). Mild stress experiences can set up psycho-neuro-immune-endocrine (PNIE) preparedness and resiliency to stress disorders.

The results of a separate series of studies in rats and the clinical trials on humans indicate that even a genetically predisposed stress response (juvenile onset diabetes) can be overridden when early immune stressors are mildly applied. In this study, Freund's adjuvent solution was injected in small amounts as the mild immune stressor. Fruend's adjuvent is regularly used with injections in order to facilitate a mild immune response. The stress "inoculated" rats do not develop their

genetically pre-programmed diabetes (Sadelain, Qin, Sumoski, Parfrey, Singh, & Rabinovitch, 1990). The mechanism of action is still being investigated (Rabinovitch, Suarez-Pinzon, Lapchak, Meager, & Power, 1995).

The psychoneuroimmunological (PNI) research literature reports numerous studies of classical conditioning of the PNI systems. The PNI classical (Pavlovian) conditioning research usually begins with the seminal work, "Conditioning phenomena and immune function" by Ader, Grota, & Cohen (1987). Mice were conditioned to produce an immune response when the scent of camphor was presented. The classically conditioned mice were able to resist immune infections with the camphor stimulated immune system response. Classical conditioning can be used to activate or inhibit responses, by accessing the plasticity of the stress system responses. The therapeutic application of classical conditioning of each area of the stress response PNIE systems is theoretically possible. Therapeutic conditioning would be done prior to severe stress to expand the stress response repertoire and prevent or reduce severe responses to stress. Only a few sources are beginning to acknowledge the intercommunicating PNIE pathways and the need to address the parts as an integrated whole (e.g., Pert, 1986; Meaney, 1993; Sapolsky, Krey, & McEwen, 1986).

Contrada, Leventhal, and O'Leary (1990) recognize the new advances in peptide changes as a part of the stress response and suggest that this added understanding of complexity and specificity encourage us to look for a new holistic model. They are quoted (in Pervin, 1990, p. 643) as follows.

> At one time the defensive activity of the immune system was thought to be stimulated only by bacterial or viral agents. Rapidly accumulating evidence has made it clear, however, that defensive actions

> by the immune system are influenced by activity in the [sympathetic-adrenomedullary] SAM, [the pituitary-adrenocortical] PAC, and peptide systems, all three of which are linked to emotion, stress, and pain. Because the three communicate with one another and with the immune system, Pert (1986) has suggested that they constitute a single system. This conclusion requires that we alter our view of the cognitive-emotional interactions and their correlated physiologic processes.

They recommend that we envision the brain and body, each with its own hormone receptors and hormone producers, which are bathed by similar biochemicals, but produce different, yet intercommunicating effects (Pervin, 1990, p. 644). The views on the nature of stress responses and pathways are changing in this direction.

There is some agreement on the nature of the stress symptoms and stressor factors from the new DSM-IV changes for PTSD. Gabbard (1994), writes that PTSD will remain in the same stress response category with anxiety in the DSM-IV edition, despite the unanimous vote by the DSM-IV Advisory Subcommittee to classify PTSD in a new stress category. The maintenance of the *status quo* remains despite the fact PTSD differs from anxiety as a response to stress by having its own constellation of symptoms, only one of which may include anxiety. PTSD is also believed to require predisposing factors (psychological and/or physiological), caused by earlier stress experience. For example, "In the Detroit study (Breslau, David, Andreski, et al., 1991) it was determined that the risk for developing PTSD could be linked to early separation from parents, neuroticism, family history of anxiety, and pre-existing anxiety or depression" (Gabbard, 1994, p. 275). Gabbard (1994) also mentions the studies of treatment difficulties due to, "long-term

neurobiological alterations in noradrenergic and serotonergic functioning, the hypothalamic-pituitary-adrenocorticol axis, the endogenous opiod system, and the diurnal sleep cycle [which] have led researchers to try to identify a specific medication that could address these [persistent] changes" (p. 277). Thus, there are indications of prior exposure to stressors leading to PNIE changes that persist (and are maladaptive) described in the research literature for some mental illnesses.

There is a paucity of research on the physiological alterations or identifiers that set these previously stressed or predisposed individuals apart. Are the previously stressed individuals identifiable as vulnerable before the next trauma that could precipitate PTSD or another stress disorder? It is the contention in this thesis that there is enough animal and human research data (only some referenced in this thesis) to suggest that mental health and medical healthcare providers could study further ways of improving preventative therapies. This may be accomplished by using stress response indicator patterns (e.g., cortisol production, cortisol receptor numbers, heart rate reactivity, catecholamine levels) as predictors of vulnerability or resiliency to stress response disorders. It is feasible to seek vulnerability identifiers from individual and group stress response repertoires (i.e., physiological and/or behavioral indicators) (e.g., Hertsgaard, Gunner, Erickson, & Nachmias, 1995; Kagan, 1989; Post, 1992, Meaney, 1993; Yehuda, Resnick, Kahana, & Giller, 1993; Spangler & Grossmann, 1993). For example, high glucocorticoid receptor numbers and low glucocorticoid production levels measured in the blood could be indicators of resiliency to stress disorders and worthy of a future research focus in prospective studies of humans in order to identify how to facilitate this type of resiliency.

A study of PTSD in holocaust and war survivors provides a comparison

between their psychosomatic symptoms and particular stress responses. Krystal (1988) found that these victims usually suffer from alexithymia- the inability to identify or verbalize feeling states. They are not able to use emotions as signals for self awareness and understanding, nor can they communicate and interact with emotions. Alexithymics are unable to self-soothe and many resort to chemical dependency for somatic complaints (Krystal, 1988; Khantzian, Halliday, & McAuliffe, 1990). While there is evidence that neuro-endocrine alterations are found correlated together after trauma (Mason, 1974, 1975a), there is less human data indicating whether these factors can be found as vulnerabilities before the major trauma (demonstrated in the research conducted by Yehuda, et al., 1993). All the research discussed above provide examples of plasticity which can result in resiliency or vulnerability to stress disorders. In many of the above cases this psychobiological plasticity in early development leads to persistent changes which become more difficult to alter (but not impossible, Rossi, 1987) later in adult human life.

Chapter 6: States, Traits, and Types of Stress Responses

States, traits, and types of stress responses are the topics of this chapter because these concepts frequently appear and require clarification in studies of stress responses. These three concepts will be defined according to a hierarchy. Beginning with "states, as singly occurring or habitual behaviors" (e.g., sleep, awake, talkative) (Eysenck, 1990, p. 244). Next, a trait can be defined "in terms of significant intercorrelations between different habitual behaviors" (Eysenck, p. 244) or intercorrelated states. For example, Kagan's (1988) understanding of inhibition or shyness is called a trait because it consists of significant intercorrelations between different states or behaviors (e.g., quiet, socially restrained behavior or less talkative and less affective). Types are then defined "in terms of observed intercorrelations between traits" (Eysenck, p. 244). For example, Eysenck used this definition for the personality types Extravert, Introvert, Neuroticism, Psychoticism. "Thus 'extraversion' is defined by the observed correlations between sociability, liveliness, activity, assertiveness, dominance, surgency, and so on" (pp. 244-245). Such correlated traits were grouped according to their relatedness and labeled as the type -"extraversion". The intercorrelation of traits which occur externally will be called Externalizer traits or the traits which occur internally will be called Internalizer traits in order to distinguish along a continuum of two opposing types of stress responding individuals (see diagram and earlier discussion on p. 15). In order to distinguish "prostress" responses from traumatized or deprived responses, the constructs of Internalizing (physiological) and Externalizing (behavioral) responses were designed to distinguish among measurable types of stress response patterns observed in individuals (described next).

Peters and Landers, (contacted by personal communication) involved in

stress research on neonates at the University of Alberta, acknowledged that neonates differ in internal (i.e., physiological) and external (i.e., behavioral) responses. Peters' (1995) research on pre-term neonates suggest that out of fourteen babies selected for a study of behavioral and physiological stress responses during hospitalization, two neonates (subjects #301 & #208) had more responses either internally or externally than the remaining twelve. This research data may indicate that Internalizer and Externalizer types of stress responses in neonates exist. Within this thesis, a continuum is proposed for neonate stress responses (briefly diagrammed in Fig. 1 in the Introduction).

Peters and Landers were able to recall exemplar cases from hospitalized neonates with: 1) little responsiveness to stress that was externally observable and yet a physiological crisis (e.g., increased heart rate, reduced oxygen saturation) was noted internally or 2) the other extreme, was a great deal of motor activity (e.g., crying and arm waving) in an external stress response to a present stressor, while little physiological disruption occurred. Typically, most neonates exhibit some degree of both internal and external cues (Peters, 1995; Als, 1986). The suggestion made in this thesis is that a consistent pattern of stability in Externalizer and Internalizer responses to stress can be found soon after birth in the healthy neonate. Similar types of stable traits in neonate and infant responses to stress have been researched by other authors (e.g., Kagan, 1989; Thomas & Chess, 1984; Fox, 1989; Tennes, Kreye, Avitable, & Wells,1986, Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995; Hertsgaard, Gunnar, Erickson, & Nachmias, 1995). The neonate's ability to control stress with external (motoric) means of behavior before an internal physiological crisis occurs is considered a sign of neurodevelopmental maturity. On the other hand, a physically immature (premature) neonate may attempt to correct for physiological crises with after the fact changes of behavioral

and arousal states (e.g., Peters, 1995; Als, 1986). A similar mature or immature type of response to stress may persist into adulthood and not necessarily continue to develop or improve.

When does the stress response begin? Numerous studies have demonstrated stress responses in the human fetus (Ruel et al., 1994; Anders & Zeanah, 1983). Do stress responses go through developmental changes? Most likely yes, with sensitive or critical time periods for neural, immune, and endocrine systems. When do stress responses persist or stabilize, becoming more trait-like (according to the definition of trait on p.) patterns of stress responses? Overwhelming experiences of acute and/or chronic stress can lead to a regression or decompensation even in adult victims (Gabbard, 1994). This is usually a temporary state but in many PTSD patients it appears persistent or enduring. If the mind cannot alter the stress intensity then it seems to become internalized into psychosomatic disorders. However, the trait-like quality of PTSD (noted by Pitman, 1993; Shalev, Rogel-Fuchs, 1993; Yehuda et al., 1993; Nemiah, 1977) and the related trait-like response patterns of alexithymia (noted by Hyer, Woods, & Boudewyns, 1991; Taylor, Bagby, & Parker, 1993) have led these researchers to question what these individuals' stress responses were like before the trauma. Alexithymia, or the inability to find words for emotions causing emotional arousal to be expressed at a somatic level, is commonly found among PTSD sufferers (Krystal, 1988; Hyers et al., 1991). When found together, PTSD with alexithymia, the risk of suicide is significantly increased and Hyer and colleagues comment "It may be said that alexithymics are at greater risk for developing PTSD" (p.132). And ". . . One might speculate that suicide and alexithymia coexist among this group [of PTSD sufferers] because there is no 'outlet' for the [relief of] emotional intensity" (p. 135). Hyer and colleagues findings support the postulation in this

thesis that Externalizers may be less vulnerable to PTSD and other stress related disorders, than Internalizers who may be found with higher rates of alexithymia and stress disorders like PTSD, substance abuse and psychosomatic disorders which are all commonly found together according to Krystal, 1988; Khantzian, Halliday, and McCauliffe, 1990).

United States military medical records were used to trace measured stress levels of PTSD war veterans prior to the war trauma. In this research, Pitman (1993) describes hyperactive sympathetic stress responses (i.e., higher baseline heart rate and blood pressure) in PTSD victims compared to control subjects after trauma and a hypoactive (lower heart rate) or otherwise normal stress responses before the trauma. Other research data support the normal to lower than normal baseline heart rates in adult PTSD models (Yehuda, Resnick, Kahana, & Giller,1993). In other words, baseline measures have been found to be within normal ranges in some test subjects with stress disorders. It is the immediate and recovery responses to specific stressors that the measurement ranges differ. The stress responses in humans have been found (retrospectively) to differ in the measurements between those individuals who have stress disorders (considered vulnerable) compared to those individuals without stress disorders (considered resilient) (Hyer et al., 1991; Yehuda et al., 1993; Gunnar et al., 1995; Hertsgaard, 1995; Jemerin & Boyce, 1990).

It has been discussed in this thesis that individuals vulnerable to stress disorders have experienced either too little stress stimulation (deprivation) or too much stress stimulation (trauma), rather than good-enough / appropriate stress stimulation ("prostress"), which is also influenced by the individual's stress response type and developmental stage. "Prostress" will likely require mild forms of distress. The word "mild" is relative; what is mild for a hypersensitive individual

differs from a hyposensitive individual. For example, neonates cry (this expression of the neonate's stress can be called distress and not all sources of distress should, or can, be stopped immediately) but some cry more easily and longer than others, over what seems like a mild stressor to an attentive observer.

It is proposed in this thesis, based on the research discussed (above) by Plotsky et al. (1993) and Yehuda et al. (1993) that some individuals do not develop a stress response system capable of handling stressors effectively. Such individuals can become more vulnerable to future stress disorders. Plotsky et al.'s (1993) severely stressed rats showed greater vulnerability to viral infections as adults. These rats as adults also took longer to recover from the viral infection. Similarly, Yehuda et al.'s (1993) PTSD patients who were considered vulnerable to stress demonstrated higher stress responses (i.e., cortisol production) and longer recovery times (i.e., lasting cortisol levels over time). As well, Hertsgaard et al.'s (1995) and Gunner et al.'s (1995) high cortisol levels during pre-stress baseline sampling and/or during stressor administration in (human) newborns, appear to correlate later with lower cortisol levels during stress and more resilient stress responses in infants at 6 months of age. An important stipulation, supportive of this author's postulations, is suggested by Lewis and Ramsay (1995) as follows. "A developmental trend for decreased adrenocortical reactivity might be more apparent for relatively mild stressors [e.g., heelstick blood sample, maternal separation, a strange new comforting female in mother's absence, well-baby physical exam] as opposed to intense stressors" (p. 658). This could be seen as mild, good-enough "prostress" experience for many newborns who mature around 6 months with a strong, brief stress responses due to prior experience with mild stress.

It is also important to consider problems that occur with the stress

response recovery stage (including the parasympathetic rebound). This can include a recovery response to stress which is too late, too soon, too strong, or too weak after the immediate sympathetic stress response. These problematic recovery responses can increase vulnerability while presenting normal baseline responses before the stress occurs. Theoretically, after the stress occurs, the extreme deviations from the typical / average stress response levels would be detectable. "Despite a strong response [to stressors], healthy neonates recover rapidly [their behavior like crying, vagal tone, and cortisol levels]. This rapid recovery reflects the powerful self-righting processes of the healthy neonate following mild perturbations" (Gunner et al., 1995, p. 10).

During stress, the endocrine (hormone) productions from infants are expected to be higher than baseline (e.g., cortisol). Individuals with higher cortisol productions than considered normal for infants after 6 months of age can be indicative of greater overall PNIE (e.g., endocrine, hormone, and immune) reactivity in general. Wilder (1995) states that such

> unrestrained or inadequately restrained immune [reactivity] and inflammatory processes [which] may produce autoimmune disease or injury to self-tissues [e.g., swelling and edema, high fever, or the parasympathetic rebound which slows the heart after the immediate sympathetic response of speeding it up]. Conversely, neuroendocrine [hormonal] mechanisms that lead to excessively inhibited immune and inflammatory processes produce immunosuppression and its consequences [vulnerability to infections] . . . It is now clear that either an overactive or underactive response to stress may, itself, produce or contribute to disease. (p. 309)

The role of increased or decreased hormone levels associated with stress are included in developing theories which account for the evidence of gender related immune disorder vulnerabilities (e.g., up to 19 females for every male with thyroiditis, 9:1 with lupus, and 4:1 with rheumatoid arthritis) (Wilder,1995). When estrogen hormone levels increase, so does immune suppression. Thus, "autoimmune diseases tend to develop, flare, or subside during . . . times such as puberty, menses, pregnancy, the postpartum period, menopause, or in the setting of significant stress" (Wilder, p. 312). Autoimmune disorders are considered by some to be biological maladaptive responses to physiological stress, which can be exacerbated by social-emotional stressors (Asterita, 1985; Contrada, et al., 1990; Smith, 1993; Wilder,1995). Why or how stress triggers overactivity or underactivity remains under investigation.

Hormones can become endogenous stressors contributing to sex differences in stress disorders. As noted above, females are more prone to autoimmune disorders during high estrogen activity (Wilder, 1995). High androgen activity in adult males correlates with the lowest rate of autoimmune disorders (Mattsson, 1986). And fetal males, exposed to high levels of testosterone are more prone to left-hemisphere brain disorders (Mattsson, 1986), cardiovascular disorders (Frankenhauser, 1983), and immune disorders (Wilder, 1995; Mattsson, 1986) later in life. For example, testosterone suppresses thymocyte development in the immune system and "in contrast to estrogen, it suppresses humoral antibody responses" (Wilder, p. 318). Hormones can also be increased or decreased due to exogenous stressors. Wilder (1995) notes that the following statements, while simplistic and commonly stated, remain difficult to demonstrate once all the influencing variables are included. Sex hormones affect immune functioning (Baum & Grunberg, 1991), "stress processes can directly contribute to illness" (Smith,

1993, p. 123), and most hormones (including growth hormone, prolactin, insulin, and sex hormones) are stress responsive (Asterita, 1985). The interaction between hormones, stressors, and resiliency or vulnerability to stress disorders are complex and remain to be delineated.

Individuals with PTSD and those vulnerable to such stress disorders are likely to exhibit higher, longer sustained stress response levels during stress. For example, PTSD patients have higher levels of cortisol production and higher cortisol receptor numbers, quicker recovery to low cortisol baseline levels, (Yehuda, Resnick, Kahana, & Giller, 1993). The more resilient individuals have a lower, quicker stress response to a recent stressor. It seems that trauma increases the cortisol production levels and receptor numbers to be even higher than mild prior exposure to stressors which is still higher than those with little prior experience with stressors. This is related to Meaney's (1993) findings in animal subjects, where postnatal exposure to mild stress produces enough stress system receptors capable of quickly and effectively dealing with stress. The appropriate amount of stress system receptors can allow for brief, less intense sympathetic responses, quicker feedback, and brief parasympathetic (recovery) responses (see Chapter 4 for a description of the parasympathetic stress response system). On the other hand, far-too-much (traumatic) stress from past experiences (especially during early development) could produce too many stress receptors on the neurons and/or lymphocytes. This increase in available receptors can leave an individual hypo-stress responsive, due to a greater stress hormone receptor uptake, especially if stress hormone production is low (Yehuda et al., 1993).

The postulations within this thesis, about types of stress responses, pertain to those individuals who experience stress during early developmental periods

when neuroendocrine and immune systems may be more susceptible to environmental influences. We could call vulnerability to stress a genetic trait since we are looking at early 'hard-wiring', or the expression of the gene when turned on or off by environmental stimulation. However, vulnerability to stress is more than turning genes on or off. It is the gene interacting with the frequency, intensity, and variety of environmental stimuli that produce phenotypic variations among individuals. Vulnerability to stress may have more to do with the range of genetic expression and the phenotypes (observable variations) that result from genes interacting with environment. If we look at genes alone we miss the complex ways that genes interact with the environment. Genes are changeable (Post, 1992) and are necessary to produce the more persistent traits that are formed during the height of plasticity when the neurons and pathways are making first connections and responding to environmental input (Changeux, 1985; Erzurumlu & Killackey, 1982). However, it is the survival of the individual's neurons, and the connections, and receptors that are developed based on the frequency or intensity of use through environmental demands. Human research seems to support the trait-like enduring pattern of hormonal levels associated with stress response patterns. For example, Yehuda et al. (1993) state,

> In the aggregate, this research [cited below] has lead to the suggestion that hormonal levels may reflect not only state changes, such as emotional arousal or distress, but also more enduring trait or style characteristics including those linked to coping mechanisms (Frankenhauser, 1975; Funkenstein, King, & Drollette, 1954; Knight, Atkins, & Eagle, 1979; Kosten, Jacobs, & Mason; 1984; Mason, 1975[d]; Poe, Rose, & Mason;

1970; Williams, 1983; Wolff, Friedman, Hofer, & Mason, 1964). (p. 293)

In a study investigating responses to prenatal immune challenges, Reul and colleagues (1994) reported that "clinically, it may be postulated that disturbed fetal brain development due to prenatal immune challenge increases the vulnerability to develop mental illness involving inadequate responses to stress" (p. 2600). It is proposed in this thesis that the right amount of immune challenge, given at the right time, may decrease vulnerability and increase resiliency to developing stress response disorders. Examples discussed in this thesis include fast-cycling bipolar depression, PTSD, alexithymia-suicide, substance abuse, certain autoimmune disorders, juvenile diabetes, cardiovascular vulnerabilities especially related to high blood pressure complications, some of which can be developed early in life (Peters, 1991, on thesis p. 32). Hormone levels like cortisol could differentiate individuals who are vulnerable to stress response disorders from those who are resilient to stress response disorders.

Previous understandings of the immune and neuro-endocrine response systems as separate were less complex than what is currently being proposed. Researchers are now moving beyond the simplistic understanding that increasing the neuro-endocrine system responses with stress decreases the immune response. It is now possible (in animals) to change the immune system by challenging the neuro-endocrine system within two weeks after birth or changing the neuro-endocrine system by inducing prenatal immune challenge. While this research is restricted to rats (human clinical investigations are currently under investigation by Dr. Rabinovitch). It does make sense that human genes would have some flexibility to interact with the environment early in development in order to enhance human

adaptation to the extreme potential varieties of environmental demands. This flexibility to interact with environmental demands is speculated to occur *in utero* and postnatally in humans (e.g., Post, 1992; Rossi & Cheek, 1988; Janov, 1983; Laing, 1976; Lowen, 1967; Montagu, 1962; Sontag, 1960; Reul et al., 1994; Barker, 1992). While human physiology and psychology continuously adapts to environmental demands throughout the life span, as the theory of plasticity describes, there are still likely to be important windows of opportunity or sensitive periods when psychobiological systems (e.g., psychological, neural, immune, endocrine PNIE systems) are being set up and integrated. Research needs to delineate how caregivers can maximize the developmental opportunities through perinatal "prostress" experiences with stress in order to promote resiliency to stress disorders.

The term perinatal was used because there is also evidence to support the idea that maternal stress is transmitted transplacentally to the fetus causing athymic immuno-suppression and a vulnerable immune status in neonates (Spraker, 1984). For example, when wild deer were stressed by capture and confinement while pregnant the thymus activity of their neonate offspring was suppressed. Vaccinations did not activate the suppressed thymus and all the fawns died of infections due to their ineffective immune systems. Spraker believes that resiliencies and vulnerabilities begin prenatally. Dubos seems to hold a similar belief; "Prenatal, neonatal, and other early influences thus constitute a continuous spectrum through which the environment conditions the whole future of the developing organism." Research on critical and sensitive developmental periods in humans (Barker, 1992) and in animals (Reul, et al., 1994; Hubel, Wiesel, & LeVay, 1977) have shown that certain prenatal and postnatal stressors impact the

organisms' vulnerability to physical and mental illnesses and most of these authors extrapolate their data to human stress disorders. An example of this research is Barker's (1992) human research titled, "Fetal and infant origins of adult disease."

Researchers are left to contemplate whether the human time periods of opportunity for adapting physiologically remain open for longer periods than those demonstrated by a variety of other species. Lerner (1976), and other developmentalists (e.g., Hunt, 1980; Schneirla & Rosenblatt, 1961, 1963) have noted that humans are less vulnerable to critical periods than other animal species and that environmental factors continue to influence structural changes longer. For example, the following is a comparison of two animal species that are less developmentally organized than humans and thus have more genetic rigidity. The gull responds only to a dark spot on the bill of another of its species in order to feed soon after hatching. Otherwise, it fails to eat and dies (Alcock, 1989). Comparatively, a more adaptable bird species, like the goose, will imprint on the first available moving object that feeds it. This would allow for foster parenting, rather than certain death, if the hatchlings' parents die. Humans are even more adaptable and can foster to any sufficient, available caregiver. An organism's trait can be more genetically programmed or it can be more phenotypically influenced during the life span according to its responsiveness to environmental demands.

This chapter defined states and traits as concepts that describe types of stress responses. Some of the more recent research incorporating types of stress responses for investigating vulnerability and resiliency to stress disorders were discussed in this chapter. The next chapter investigates several recently emerging models which incorporate the useful effects of "prostress" exposure to mild stressors in order to prevent stress disorders.

Chapter 7: Early Prostress Conditioning for Resiliency

A contemporary model in diabetic research has been developing which strengthens the link between genetic vulnerability (Type I or Early-onset, juvenile diabetes) and environmental stressors that can either permanently prevent or initiate diabetic onset. In the diabetic model, there exists a potential to override Type I diabetes by the early distraction of the immune system with a mild external immune stressor (Sadelain, Qin, Lauzon, & Singh, 1990). In animals, this distraction only occurs during a critical period of development. In humans this distraction of the immune system may occur over a longer sensitive period of development (Dr. Rabinovitch, Diabetes researcher at the University of Alberta). A psychoneuroendocrine distraction model analogous to the above immune distraction model is hypothesized here for psychobiological resiliency to stress disorders (in animals and humans). Stress disorders may result from far-too-much external stress (trauma) to far-too-little stress (deprivation), which distracts, inhibits, or strengthens neuro-immune patterns that are forming and becoming pre-set during sensitive periods when the neuro-immune systems are most open to change or adaptation. Are we missing critical periods in early human development when we could be initiating resiliency in neuro-immune patterns and thus prevent stress disorder onset, whether genetically or environmentally induced?

The immune distraction model (just noted above) evolved at the University of Alberta, with research on non-obese diabetic NOD mice (Sadelain, Qin, Lauzon, & Singh, 1990). At least 80% of these mice could be made resilient to diabetic symptoms (i.e., the autoimmune destruction of pancreatic islet beta cells, Type I diabetes) by activating and distracting the immune system within the critical window period soon after birth with a single injection of Freund's adjuvant (a

common general immune system stimulant). These results, in turn, led to the forthcoming explanation for the puzzling epidemiological data which revealed Finland, Sardinia (Italy), and Sweden had the highest incidence of diabetes according to a collection of studies from the late eighties (Karvonen, Tuomilehto, Libman, & LaPorte for the World Health Organization, WHO; 1993). The lowest incidence was found in Asia, followed by Australia, New Zealand, South, and then North America. "Although genetic susceptibility is evidently necessary for the development of Type I diabetes, it is not sufficient to cause the disease. Thus, the unknown environmental factors must play [an] important role in promoting or at least triggering Type I diabetes" (Karvonen et al., 1993, p. 889). The "unknown environmental factors" have been elucidated by the research on the immune system alterations caused by complete Freund's adjuvant (CFA). The possibility remains to be investigated that CFA, as an immunization vehicle, was more popular in the countries with lower incidences of diabetes. It may then be found that part of the "unknown environmental factors" do not trigger Type I diabetes, instead they prevent diabetes (personal communication with a diabetic researcher).

Further research conducted at the University of Alberta investigated the protective effect of Freund's adjuvent against autoimmune diabetes in rats (Rabinovitch, Suarez-Pinzon, Lapchak, Meager, & Power, 1995). The research is an investigation of the mechanisms believed to be involved in preventing autoimmune diabetes. Rabinovitch et al. (1995) state, ". . .in NOD mice, where CFA provides more complete protection from diabetes . . . CFA is a strong immune adjuvant and is likely to have widespread effects on immunoregulatory circuits" (p. 8). Sadelain et al. (1990) wrote that the research findings, "raise the possibility that human [Insulin-Dependent Diabetes Mellitus] IDDM may be susceptible to prevention by early intervention with a clinically acceptable immune

adjuvant or other immunostimulatory agent(s)" (p. 678). A "prostress" stimulation of the generalized stress response which activates, inhibits, and/or distracts the necessary pathways (e.g., psycho-neuro-immuno-endocrine-etc.) during early development, may be effective as a resiliency inoculation or booster.

If an application of the above model is successful, it may become possible to state the following for stress disorders in general, rather than only for diabetes in particular.

> The disease process can now be identified in its early, pre-symptomatic stages [using neuro-endocrine-immune measures of stress responses and recovery] and thus, the time has come for the investigation of preventative therapies through multicenter clinical trials. A wide variety of strategies are available and their choice should be dependent on the pathogenic stage of disease at which treatment is initiated. (Muir, Schatz, Pozzilli, & Maclaren, 1993, p. 301)

This stage-specific approach to prevention is superior to offering whatever intervention for stress disorders the healthcare provider happens to deliver. The next stage is to improve identification of vulnerability, improve prevention methods, and provide treatment according to the stage of the disorder and the systems that are malfunctioning.

Rossi (1987) has proposed a relevant treatment for stress disorders. Rossi's treatment called "state-dependent reregulation", is based on similar principles of a general stress response that can activate or be rechannelled in order to de-activate stress response disruptions.

> Psychosomatic symptoms are acquired by a process of experiential learning, specifically the state-dependent learning of response patterns of the General Adaptation Syndrome [GAS, discussed in this thesis Chapter 5]. Enduring psychosomatic problems [stress response disorders] are manifestations of state-bound patterns of the General Adaptation Syndrome. . . Selye reasoned that if a shock could get one stuck in a groove, perhaps another shock could get one out again, allowing the patient to 'snap out of the disease' [Selye, 1976]. He believed that the various forms of shock - including electroconvulsive and insulin shock as well as psychological shock - were types of *nonspecific therapies* that counteracted many of the *nonspecific aspects* of the General Adaptation Syndrome. (Rossi, 1987, p. 50) [Italics placed by thesis author]

Nonspecific therapies may generally 'distract' the PNIE systems in an overwhelming, over-riding manner, somewhat like the second blow to the head restores the memory to an amnesia sufferer, in some cases. Rossi's (1987) description of "state-dependent reregulation" sounds more like specific stress disordered PNIE pathways can be reregulated, rechannelled, or de-activated in children or adults. This may be using the extended human plasticity potential.

Stress resiliency boosting has already been described in the literature. Such a technique is suggested by Rutherford and Neil (1994), in their book "How to raise a puppy you can live with". They suggest specific conditioning techniques (performed by the pet owner, in addition to normal stimulation) throughout the critical four week period (of 3 to 7 weeks of age) during puppy development. These techniques enhance future temperature, tactile, visual, auditory, etc. stress responses by exposing them to moderate ranges of stressors

(called "prostress" experiences in this thesis). The 22nd and 49th day (of the 3rd and 7th week) are the critical periods for all breeds. The authors caution that the 8th week is the "fear" week and that distress, trauma, loud noises, and novel stressors (e.g., travel) are to be avoided lest they leave a permanent fear or startle response. They explain that toy breeds are often overprotected by well-meaning owners during the critical period for enhancing stress responses. The results are spoiled, over-dependent, neotonous behaviors and a vulnerability to stress disorders.

Izquierdo (1984) and McGaugh (1983) describe research on the neurobiology of memory and learning where hormones (that are released during periods of stress) serve to modulate memory and learning in the limbic system. The limbic system includes the hippocampus and amygdala, known to mediate "short- and long-term memory, learning, and behavioral processes associated with motivation and emotion. These in turn, modulate the hypothalamic regulation of the autonomic, endocrine, immune, and neuropeptide systems" (Rossi, 1987, p. 48). Interestingly, high levels of cortisol, flooding the hippocampus and hypothalamus have been found to destroy neurons. This destruction can lead to increased cognitive impairment during aging (Meaney, 1993; Sapolsky, Krey, & McEwen, 1985). Others have noted a connection between high cortisol levels and the attenuation of active avoidance into passive avoidance and learned helplessness in animal studies. Yehuda et al. (1993), call attention this.

> In some preclinical studies, high corticosterone levels have been associated with superior passive avoidence learning [learned helplessness described by Levine, Gordon, Peterson, & Rose, 1970; Lissak, Endroczi, & Medgyesi, 1957], but not increased active avoidance [coping behavior described by

> Levine, Gordon, Peterson, & Rose, 1970; Mason, 1968]. This observation has led to the suggestion that corticosteroids [e.g., corticosterone and cortisol] may act to increase the ability of the organisms to cope with stress by normalizing [reducing / attenuating] the increased arousal [considered destructive when chronic] in limbic midbrain structures [Bohus, 1973, 1978] in response to stress. (p. 293).

This research lends further support to a postulation proposed in this thesis; that there exists a stress response process of PNIE systems which can develop resiliency from an early stage of emotional development. Such a stress response process would be activated when any of the PNIE stress response systems are activated and if an over-stimulation or understimulation occurs during activation then disorders or disruptions may result. This potentially hazardous doorway to vulnerability could be used instead, for stress disorder prevention or the promotion of resiliency.

Conclusion: An Outline for Future Research

This concluding chapter will consist of a discussion of important terms relevant to developing a research design for the research incorporating stress responses and an outline of specific research questions derived from the literature review important for understanding stress disorders. Original theoretical ideas were developed in the course of this investigation and the major ideas relevant to future research are listed and summarized (see Summary, following the Conclusion). Stress research needs direction (suggested in this thesis) in order to provide caregivers with valuable prophylactic measures in order to prevent stress disorders and promote resiliency. What are some valuable prostress experiences and how can caregivers best apply these to promote resiliency to stress disorders early in human development? This is the intended focus of the following suggestions for future research.

Discussion of research terms

Different types of stress responders can be identified according to their various constellations of traits (e.g., *sensitizers*, *repressors*). It is necessary to define and defend the two types of stress responders (Internalizers or Externalizers). According to the physiological and psychological traits involved, an Internalizer is a person who tends to give more internal physiological responses (e.g., heart rate, blood pressure, cortisol release) and less behavioral, affective, or cognitive expression to a specific physical, psychological, or social stressor. An Externalizer is the opposite; a person who tends to express a specific stressor externally, with more verbal and less physiological responses. According to this research construct, which proposes a spectrum of types of subjects and correlated traits that can be measured, one individual could respond to most stressors with Internalizing, physiological responses, another with Externalizing, expressive

responses. Because the construct is modeled on a continuum, other individuals could present with varying degrees of both (see Fig. 1, on p. 15). Meanwhile, the intensity of the specific response must also be considered. For example, an Internalizer could hyper-respond to one kind of stressor (physically stimulating) and hypo-respond to another stressor (emotionally stimulating).

The reason for using Internalizer and Externalizer instead of other, more popular terms found in the literature is two-fold. First, the other terms (i.e., *sensitizers-repressors, introvert-extravert, reactivity, stimulus seeking-avoiding, inhibition*) limit the variety of responses and the specific pathways they define. We need a broader, more comprehensive set of terms to expand and clarify our construct. Two examples of such limitations follow: 1) the terms *introvert-extravert* require the addition of *neuroticism* and *psychotocism* to describe the range of traits studied (Eysenck, 1990); and, *reactivity* is limited to the response style of the highly sensitive individual who avoids stimulation and arousal without offering a term for the opposite (Kohn, 1985, 1991; Strelau, 1983); 2) a *repressor*, has been defined as one who is unable, or prefers not, to express the physiological stress responses happening internally (Byrne, 1961); but this does not explain whether they will have more physiological activity than the *sensitizer*, or that the *sensitizer* will have less.

For this thesis, the search was for a construct based on a continuum which would clarify the following points.

- Are there individuals who tend to have more internal physiological responses to stress and do they present less external awareness or verbal expression?
- Are they Internalizers who are more prone to physical, substance abuse, depression, and anxiety disorders when exposed to stress?

- Do Externalizers tend to express their stress verbally and emotionally?
- Do they have less severe physiological and psychosomatic responses as a result?
- Are they more prone to behavioral and cognitive disorders?
- Can Internalizers and Externalizers be found with primarily hypersensitive responsiveness to stressors or hyposensitive responsiveness?
- Can some individuals be found with equal amounts of Internalizing and Externalizing traits?
- If an individual has a neuro-endocrine malfunction from before birth (due to a genetic difference or a developmental insult) or an acquired malfunction after birth (due to an environmental insult), is there a tendency to respond to stress more as an Internalizer, or less (physiologically) as an Externalizer?
- When stress is severe or chronic, do Internalizers incur a serious physical or mental stress breakdown?
- Do they avoid additional internal physiological disruption (e.g., withdraw, freeze), or turn externally to indirect behavioral responses (e.g., addictions, etc.) or unexplained affective responses (e.g., depressions, anxieties, etc.) to alleviate stress?
- Does the Externalizer turn more quickly to external verbal and/or direct behavioral expressions (e.g., anger, fight, flight) of response, even when stressors are mild?

Answering these questions through future research may help identify types of stress responses in individuals who are vulnerable or resilient to developing stress disorders. It would be most interesting to research how early in human development persistent patterns of stress responses can be identified, whether or not stressors can alter the stress response patterns, and if so how easily through

out the human life span.

The second reason for not using the popular terms listed above for stress response types is that they all describe qualitative results without including a complete profile of the psychobiological pathways and systems involved. It is important to organize all the relevant responses to stress that these terms measure in order to design a research stress response profile. This may provide a framework to differentiate resilient or vulnerable stress response patterns. The popular terms (e.g., Extravert, inhibited, sensitizer) identify only a few levels of stress responses (i.e., the physiological, physical, behavioral, cognitive, affective). Explanations for why one response takes priority over the others need to be provided. Rarely are these explanations found in the literature. For example, why is the stress related skin-conductance levels of repressors more relevant than measuring their heart rate or cortisol levels? Why not include a more complete stress response profile? Some researchers are calling for the inclusion of more responses and traits. However, certain responses and traits are left out without explanation (typically, the parasympathetic rebound). It is also important to explain why the stress responses which were selected were included.

Kagan (1989) lists heart rate, pupillary dilation, norepinephrine levels, vocal cord muscle tension, and salivary cortisol, as the important psychobiological stress measures; Jemerin & Boyce (1990) list heart rate and blood pressure. Gunner, Porter, Wolf, Rigatuso, & Larson (1995) recommend using vagal heart tone, cortisol levels, and behavioral responsivity to stressors in order to get a more accurate picture of the individual's reactivity to stress. These indicators, used in research, account for only a small portion of the acute, sympathetic stress responses and typically do not include the parasympathetic recovery stress response (e.g., vagal tone / heart rate reactivity) or the SAM axis, PAC axis,

immune, or peptide pathways and feedback loops. The proposal developed here is that researchers need to look at a more holistic profile of an individual's stress response pattern, recovery repertoire, and baseline resting levels to better identify specific areas of malfunction.

Therapy that addresses psychobiological principles could become more effective by incorporating the above approaches for identifying the how and why of stress response disorders. Furthermore, in speculation of a future course for therapy, why treat a biological stress disorder cognitively if biochemical advances have proven more direct and effective under specific circumstances? On the other hand, if cognitive or hypnotherapy is effective at overriding misperceptions or maladaptive memory states, biochemical treatment would be less appropriate. Ideally, prevention should be chosen over treatment, whenever possible. The current wide variety of therapeutic approaches used for treating stress disorders described in the literature may be due, at least in part, to the lack of one method or approach being proven more effective. There is still much work to be done in order to identify and understand the internal biological and the external psychological changes of stress response disorders.

Beyond the PNIE stress response levels discussed above, there are terms used for describing clusters of traits which are used in this thesis; hyper- (more) or hypo- (less) stress responders, either of which can apply to Internalizers or Externalizers. Different frequencies, durations, and intensities of responses can occur in one individual. The Internalizer - Externalizer stress response type construct should be designed into research that accommodates the following data. Some neonates are hyper-stress responders, either internally, externally, or both. Other neonates are hypo-stress responders, internally, externally, or both. These variations in types of stress responses / responders could be assessed before and

after the independent variables were applied as treatment. The assessment of types of responders is described in the next paragraph. Treatment may consist of: (1) a brief noxious stimulation or a 'mild' stress experience, (e.g., according to the caregivers' interpretations of 'mild', a neonate PKU blood test, or a childhood inoculation, or a brief separation from the primary care-giver, etc.); (2) a 'severe' stress experience or a prolonged noxious stimulation (e.g., circumcision, elective surgery, observational-hospitalization which causes longer-term separation from family, etc.). Responses should be measured in terms of which pathways are impacted, their frequency of cycling / reactivity, or duration / length of activity, intensity / level of production, and speed recovery / negative feedback.

To better define the limits of the postulations suggested in this thesis, fitting them into a concise research design with clear hypotheses, it is necessary to identify neonates with an Internalizing repertoire of stress responses and those with Externalizing repertoires from among a large population of newborns. This could be achieved by measuring healthy newborns' responses at baseline, during stress, and after stress (the recovery response). Assessment measures could be made using physiological responses (taking measures of salivary cortisol levels, heart rate variability, blood pressure, and urinary catecholamine levels), behavioral (using Peter's (1991) motoric / behavioral response list), and temperamental responses (using Thomas, & Chess (1984) temperament descriptors). These measures could be taken during specific physically and emotionally stressful procedures typically found in the child health care clinics and hospitals. Procedures may include mild to severe stressors (e.g., newborn bathing procedures, immunizations, elective surgery, accident or trauma recovery, etc.). Ideally, a stress response profile (of psychobiological stress responses from the behavioral, neural, immune, and endocrine indicators) could be measured to

determine if any changes occur, how much of each occur, and what kind of persistent changes occur. This may enhance the current understanding of the human plasticity potential for stress response variety or answer what are prostress experiences, and what are important aspects of resilience and vulnerability to stress disorders.

Outline of primary questions for future research

1) What persistent physiological changes can be found in neonates monitored before and after mild, severe, and no significant stressors?

2) If neonates are identified as Internalizers and Externalizers, are they born with these correlated identifiers or traits and/or do they acquire them?

3) Does severe stress effect the neonate stress response repertoire?

4) Does severe versus mild stress alter the neuro-endocrine stress response or recovery pathway?

5) Does low cortisol production (HPA axis = PAC axis), high noradrenaline production (SAM axis = sympathetic response), or high heart rate reactivity / vagal tone (SAM axis recovery = parasymapthetic response) correlate positively with Externalizer traits? Do any of the opposite production levels: high cortisol, low noradrenaline, or low heart rate reactivity / vagal tone correlate with Internalizer traits? (See thesis p. 65, Jemerin & Boyce, 1990)

6) Do any of the neonates with Internalizer traits, and the correlated hormonal production and recovery levels of (stress response) vulnerability develop alexithymia? How soon? Do alexithymics have Internalizer traits and the hormonal production levels of victims of prior trauma? (See thesis p. 43, Krystal, 1988)

7) Do high cortisol receptor numbers, low cortisol (mean) levels in the urine, blood, or saliva, and high cortisol production initially (soon after recent stressor) identify / correlate with resiliency to stress response disorder?

Do the opposite cortisol levels: low cortisol receptor numbers, high cortisol levels in the urine, and low cortisol initial production correlate with vulnerability due to little prior stress experience? Do high cortisol receptor numbers; high cortisol initial production; and high but slowly reduced cortisol levels in the urine correlate with vulnerability due to prior traumatic stress experience? (See thesis p. 37, Yehuda et al., 1993) This could be done by collecting blood, urine, and saliva samples from birth to adolescence, and longer if possible. Meanwhile, during sample collections, record Internalizing / Externalizing responses, hyper- or hypo-sensitivity responses, and any traumatic or deprivation experiences since last annual healthcare visit.

8) Can glucocorticoid (cortisol) receptors numbers found on lymphocytes provide memory traces of prior exposure to hormonal stress for the HPA axis in a way similar to the immune systems memory T lymphocytes found as traces after prior exposure to immune stress? Do both of these systems operate on similar principles, such that memory traces prepare the body and brain for another specific stressor attack with a readiness to reduce the depletion of body resources? The presence of too much cortisol circulating for too long in the brain and body has been connected to hypercortisolemia and hippocampal neuronal death, affective and cognitive impairments, and medical illness (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; McEwen, Gould, & Sakai, 1992; Meaney, 1993; Yehuda, Resnick, Kahana, Giller, 1993; Sapolsky, 1992). This could be analogous to the circulation of too many antigens for too long and the severe drain of resources this causes. (See thesis p. 33, Mason, 1975a)

9) Do high cortisol production levels and high glucocorticoid (cortisol) receptors numbers found on lymphocytes in the blood provide 'memory traces' of

prior experience with severe stress (as found with "vulnerable" PTSD Vietnam war veterans, holocaust survivors with PTSD, and rape survivors with PTSD, Yehuda et al., 1993)? Do high cortisol receptor numbers but low production of cortisol provide evidence of prior experience with "prostress" (appropriate, mild exposure) as found with "resilient" non-PTSD veterans, holocaust, and rape survivors? What pattern of cortisol levels correlates with no-prior experience or deprivation of experience? Theoretically, this is predicted to cause high cortisol levels, circulating for a long duration, with very few cortisol receptors. (See thesis p. 33, Plotsky et al., 1993)

There are various levels (internal or external responses) and dimensions (time periods, like prenatal, postnatal, infancy, childhood, etc.) to the Internalizer or Externalizer stress response construct. This construct has been extensively defined in this chapter in order to elucidate the postulated development of a stress response system which begins forming perinatally and provide a focus for research to measure stress response types. The PNIE stress response systems are postulated to include a process which this author has suggested is analogous to the immune system. The immune stress responses acquired through the development of immunity which are most accessible early during childhood development are suggested to be similar for the general stress responses of the PNIE systems. For the same reasons that we offer childhood immunizations (to build immune resilience during an optimum developmental period) it is proposed here that we consider building stress response resiliency for the whole PNIE system which is interconnected. The internal brain-body, psycho-neuro-immune-endocrine pathway responses to stress may each be appropriately stimulated during key developmental periods. Each system could be monitored and assessed for "prostress" experiences during the important time frames yet to be determined. Assessments include

monitoring the patterns of physiologically activated or inhibited target organs and systems (e.g., heart rate variability, hormone and receptor variability, blood pressure changes, pupil dilation, and other somatic aspects). Then come the various external responses to stress like the motoric or body movements of neonates; the more complex behaviors of infants; the affect / emotions; and expressed, cognitive / thoughts (reported by children, adolescents, and adults). These could be simplified into rating patterns over time (measures could be taken 10 - 15 minutes before, during, and up to 60 minutes after) of more Internalizing responses or more Externalizing responses to stressors and at baseline (during little or no stress).

The findings from the literature examples and research findings and extrapolations discussed in the previous chapters are suggestive that healthcare providers can improve prenatal and postnatal care techniques to provide appropriate stress experiences according to the individualized needs of neonates. Neonates can behaviorally and/or physiologically demonstrate their individual stress response vulnerabilities and resiliencies to stress disorders. Healthcare providers need to understand stress response systems and indicators in order to appropriately assess and identify neonates who are vulnerable to stress disorders.

This thesis discussed research which suggests that resiliency to stress disorders can be enhanced by early and appropriate stress experience delivery (Meaney, 1993; Plotsky et al., 1993). In other words, our early exposure to individually and developmentally appropriate stress experiences (including prenatal exposure) can enhance our resiliency to childhood, adolescent, and adult stress disorders. The importance of appropriate early stress experiences can not be underestimated. If we can promote resiliency to stress disorders through prevention techniques, then we can reduce the costs of healthcare in terms of the

increased quantity of available resources and of the increased quality of lives.

The research data supports an awareness of the impact of early childhood stresses (traumas) on later adult life. This awareness is now being described in terms of psychobiological processes and mechanisms. The groundwork has been laid and growing evidence is now available for inspection and analysis. Now is the time to investigate the prevention potential and methods for the reduction of stress disorders in humans.

Summary

The key points discussed in this thesis are as follows:

- Prenatal and neonatal exposure to some stressors may lead to resiliency or vulnerability to stress disorders.
- Neonates behaviorally and physiologically demonstrate their individual stress repertoires.
- Some neonates may demonstrate stress more or less than other neonates and could be categorized as hyper- or hypo- sensitizers.
- Some neonates demonstrate stress more internally or externally and could be categorized as Internalizers or Externalizers, or some combination of both.
- Stress indicators like salivary cortisol levels and heart rate reactivity need to be validated as reliable indicators of stress in neonates, adolescents, and adults.
- Alexithymia requires further investigation as an inability to express stress and emotions. Alexithymics report more somatic complaints and substance abuse. Alexithymia may be predictive of Internalizers or Internalizers may predict Alexithymia. Are neonates with Internalizing and trauma more prone to Alex.?
- Internalizers may be more vulnerable to stress disorders, especially as neonates.
- Evidence exists which demonstrates that some adult survivors of traumatic experiences develop alexithymia and/or posttraumatic stress disorders. It is suggested that even adult onset stress disorders were influenced by the prior establishment of stress vulnerability earlier in life.
- Chronic stress or severe acute stress may cause changes to the adult stress response pathways leading to vulnerability to stress disorders.
- Identifying a neonate's or child's stress response style (by using cortisol levels and heart rate reactivity) and adapting caregiving to the individual's needs may lead to increased resiliency.
- Identification of individual stress requirements and tolerances may improve the preventative treatment method of applying appropriate stress levels at appropriate developmental ages for the enhancement of resiliency.

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Glossary of Terms & Concepts

In order to clarify the intent and content of this thesis, the following definitions of terms and concepts will be used throughout. These definitions reflect an intensive evaluation of the stress literature (see References) as well as this author's perspective.

Stress- the organism's experience of or it's reaction to physical, physiological, and/or psychological change, with or without conscious awareness. "A physiological reaction, or response, regardless of the source of the reaction" (Everly, 1989, p. 6). The "sum of all nonspecific changes (within an organism) caused by function or damage" (Selye, 1956).

Stress response- an organism's reaction to a stressor or an organism's physical, physiological, and/or psychological change to an internal or external source. It seems that the experience of stress is general when arousal in the brain is activated and the stress is perceived by the brain. The stress responses can become increasingly more specific as more than neuronal responses of arousal are included and specific organs are targeted (inhibited or activated). Specificity is influenced by many factors, especially quality and quantity of the stressor, increasing frequency / chronicity or intensity - acuteness, and the individual's reception, perception, and interpretation of the stressor. This thesis adds the factor of prior experience with and structural changes due to this apriori stress.

Distress- unwanted, negative, or unpleasant physical, physiological, and/or psychological change.

Eustress- wanted, positive, or pleasant physical, physiological, and/or psychological change.

Stimulation- the process of the body or brain receiving or perceiving a stimulus through the activation or inhibition of one or more nerves or neurons.

Stressor / stimulus- the cause of physical, physiological, and/or psychological change which may be internally derived (e.g., from a disease or upsetting thought) or externally derived (e.g., light, heat, sound, touch, scent) with or without conscious awareness. A stressor is always a stimulus, while a stimulus is not necessarily a stressor. Some externally derived stimuli do not become stressors due to the fact that some stimuli are received by the brain but filtered out and thus are not completely perceived. Some stimuli are not intense enough to become stressors.

Stimulant- anything that causes a stress response. For example, "Coffee, tea, amphetamines, and even exercise, to mention only a few, all possess inherent . . . qualities and will induce a stress response regardless of one's interpretation of them" (Everly, 1989, p. 7).

Plasticity- the capacity of the body or brain to change or develop a biological process or pattern, whether temporary, persistent, or permanent. It is the flexibility of an organism to adapt or maladapt by using a physical, physiological, and/or psychological change. Plasticity includes the increased potential of the phenotypic expression of genes which occurs when more than one expression is possible. Each expression is then determined by previously experienced environmental stimuli and the potential for the organism to respond with variety. The degree of plasticity can affect the organism's potential for resiliency or vulnerability. Lerner (1986) explains that plasticity "is the ability to show varying responses to the same stimulus input; . . . the more plasticity shown in an organism's development, the higher the organism's psychological level" (p. 155). However, plasticity is considered a "declining phenomenon across the life span" (p. 206).

Neonate- an infant from birth to 4 weeks of age (Mosby's Medical & Nursing Dictionary, 1986)

Nerves- specialized tissues that carry electrical and/or chemical impulses and are activated or deactivated by stimulation from outside or inside the organism's body.

Neurons- nerves found in the brain.

Deprivation- little or no stimulation to activate or inhibit neurons in the brain and nerves in the body, potentially leading to pathological processes or conditions.

Trauma- a severe or intense experience of stress that activates or inhibits neurons in the brain and nerves in the body and potentially leading to pathological processes or conditions.

Inappropriate stress or stimulation- physical, physiological, and/or psychological change-a mismatch between the stress or stimulation and the organism's readiness.
that occurs at a time when the body or mind can not receive or use it constructively. A mismatch between the stress or stimulation and the organism's readiness.
For example, a child should not be taught or trained when over-tired or over-hungry because learning is not facilitated during these states.

"Prostress" (a term created for this thesis)- appropriate stress or stimulation resulting in a match between the stress or stimulation and the organism's developmental readiness to perceive and then learn from the experience.

Stress Disorder- an illness, disease, or a pathological state that follows an organism's chronic or acute experience of stress and includes an over- or under-active stress response. Several examples are posttraumatic stress disorder, ulcerative colitis, autoimmune disorders (e.g., lupus, rheumatoid arthritis, Type I diabetes).

Resiliency- a protective state when an organism is less prone or not prone to stress disorders.

Vulnerability- a relatively unprotected state when an organism is prone to stress disorders.

A pre-existing predisposition or an environmentally induced change in the brain-body processes that can leave the individual susceptible to developing stress or illness (Jemerin & Boyce, 1990).

Primary stress response- the organism's brain and body readiness, alert, and preparedness for a behavioral responses to a stressor.

Secondary stress response- the organism's behavioral and cognitive response to a stressor (e.g., to freeze, ignore, fight, flea).

Hyper-sensitive responsive - an organism with a greater or more sensitive responsiveness to stimuli or stressors than most others of its kind.

Hypo-sensitive responsive - an organism that is less sensitive and/or responsive than most others of its kind.

Internalizer - an organism that has more physiological stress responses than behavioral.

Externalizer - an organism that has more behavioral stress responses than physiological.